PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07D 207/09, 207/14, 211/34, 211/56, A61K 31/40, 31/435, A61P 29/00, 37/00

A1

(11) International Publication Number: WO 00/69815

(43) International Publication Date: 23 November 2000 (23.11.00)

(21) International Application Number: PCT/US00/06714

(22) International Filing Date: 12 May 2000 (12.05.00)

(30) Priority Data:
09/310,975 13 May 1999 (13.05.99) US

(71) Applicants (*for all designated States except US*): TEIJIN LIMITED [JP/JP]; 6-7, Minamihommachi, 1-chome, Chuo-ku, Osaka-shi, Osaka 541-0054 (JP). DUPONT PHARMACEUTICALS RESEARCH LABORATORIES [US/US]; 4570 Executive Drive, Suite 400, San Diego, CA 92121 (US).

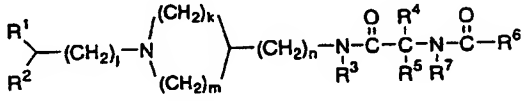
(72) Inventors; and
(75) Inventors/Applicants (*for US only*): SHIOTA, Tatsuki [JP/JP]; Teijin Limited, Tokyo Research Center, 3-2, Asahigaoka 4-chome, Hino-shi, Tokyo 191-0065 (JP). FURUYA, Minoru [JP/JP]; Teijin Limited, Tokyo Research Center, 3-2, Asahigaoka 4-chome, Hino-shi, Tokyo 191-0065 (JP). IMAI, Minoru [JP/JP]; Teijin Limited, Tokyo Research Center, 3-2, Asahigaoka 4-chome, Hino-shi, Tokyo 191-0065 (JP). SAKAI, Mitsuru [JP/JP]; Teijin Limited, Tokyo Research Center, 3-2, Asahigaoka 4-chome, Hino-shi, Tokyo 191-0065 (JP). MUROGA, Yumiko [JP/JP]; Teijin Limited, Tokyo Research Center, 3-2, Asahigaoka 4-chome, Hino-shi, Tokyo 191-0065 (JP). SUDOH, Masaki [JP/JP]; Teijin Limited, Tokyo Research Center, 3-2, Asahigaoka 4-chome, Hino-shi, Tokyo 191-0065 (JP). TARBY, Christine, M. [US/US]; 5 Spencer Lane, Hockessin, DE 19707 (US). SAIAH, Eddine [FR/US]; 4435 Noble Drive, #1, San Diego, CA 92122 (US).

(74) Agents: BIGGART, Waddell, A. et al.; Sughrue, Mion, Zinn, Macpeak & Seas, PLLC, 2100 Pennsylvania Ave., N.W., Suite 800, Washington, DC 20037-3213 (US).

(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published**
*With international search report.*
*Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

(54) Title: UREIDO-SUBSTITUTED CYCLIC AMINE DERIVATIVES AND THEIR USE AS DRUG



(I)

(57) Abstract

A compound represented by general formula (I), a pharmaceutically acceptable acid addition salt thereof or a pharmaceutically acceptable $C_1$-$C_6$ alkyl addition salt thereof, and their medical applications. Since these compounds inhibit the action of chemokines such as MIP-1α and/or MCP-1 on target cells, they may be useful as a therapeutic drug and/or preventative drug in diseases, such as atherosclerosis, rheumatoid arthritis, and the like where blood monocytes and lymphocytes infiltrate into tissues.

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | |
|---|---|
| AL | Albania |
| AM | Armenia |
| AT | Austria |
| AU | Australia |
| AZ | Azerbaijan |
| BA | Bosnia and Herzegovina |
| BB | Barbados |
| BE | Belgium |
| BF | Burkina Faso |
| BG | Bulgaria |
| BJ | Benin |
| BR | Brazil |
| BY | Belarus |
| CA | Canada |
| CF | Central African Republic |
| CG | Congo |
| CH | Switzerland |
| CI | Côte d'Ivoire |
| CM | Cameroon |
| CN | China |
| CU | Cuba |
| CZ | Czech Republic |
| DE | Germany |
| DK | Denmark |
| EE | Estonia |
| ES | Spain |
| FI | Finland |
| FR | France |
| GA | Gabon |
| GB | United Kingdom |
| GE | Georgia |
| GH | Ghana |
| GN | Guinea |
| GR | Greece |
| HU | Hungary |
| IE | Ireland |
| IL | Israel |
| IS | Iceland |
| IT | Italy |
| JP | Japan |
| KE | Kenya |
| KG | Kyrgyzstan |
| KP | Democratic People's Republic of Korea |
| KR | Republic of Korea |
| KZ | Kazakstan |
| LC | Saint Lucia |
| LI | Liechtenstein |
| LK | Sri Lanka |
| LR | Liberia |
| LS | Lesotho |
| LT | Lithuania |
| LU | Luxembourg |
| LV | Latvia |
| MC | Monaco |
| MD | Republic of Moldova |
| MG | Madagascar |
| MK | The former Yugoslav Republic of Macedonia |
| ML | Mali |
| MN | Mongolia |
| MR | Mauritania |
| MW | Malawi |
| MX | Mexico |
| NE | Niger |
| NL | Netherlands |
| NO | Norway |
| NZ | New Zealand |
| PL | Poland |
| PT | Portugal |
| RO | Romania |
| RU | Russian Federation |
| SD | Sudan |
| SE | Sweden |
| SG | Singapore |
| SI | Slovenia |
| SK | Slovakia |
| SN | Senegal |
| SZ | Swaziland |
| TD | Chad |
| TG | Togo |
| TJ | Tajikistan |
| TM | Turkmenistan |
| TR | Turkey |
| TT | Trinidad and Tobago |
| UA | Ukraine |
| UG | Uganda |
| US | United States of America |
| UZ | Uzbekistan |
| VN | Viet Nam |
| YU | Yugoslavia |
| ZW | Zimbabwe |

# SPECIFICATION

## Ureido-substituted Cyclic Amine Derivatives and Their Use as Drug

### Field of the Invention

This invention relates to novel cyclic amine derivatives substituted with a ureido group.

This invention also relates to chemokine receptor antagonists that may be effective as a therapeutic agent and/or preventive agent for diseases such as atherosclerosis, rheumatoid arthritis, psoriasis, asthma, ulcerative colitis, nephritis (nephropathy), multiple sclerosis, pulmonary fibrosis, myocarditis, hepatitis, pancreatitis, sarcoidosis, Crohn's disease, endometriosis, congestive heart failure, viral meningitis, cerebral infarction, neuropathy, Kawasaki disease, and sepsis in which tissue infiltration of blood leukocytes, such as monocytes and lymphocytes, play a major role in the initiation, progression or maintenance of the disease.

### Description of related art

Chemokines are a group of inflammatory/immunomodulatory polypeptide factors which have a molecular weight of 6-15 kD and are produced by a variety of cell types, such as macrophages, monocytes, eosinophils, neutrophiles, fibroblasts, vascular endotherial cells, smooth muscle cells, and mast cells, at inflammatory sites. The chemokines can be classified into two major subfamilies, the CXC chemokines (or α-chemokines) and CC chemokines (or β-chemokines), by the common location of the four conserved cysteine residues and by the differences in the chromosomal locations of the genes encoding them. The first two cysteines of CXC chemokines are separated by one amino acid and those of CC chemokines are adjacent. For example IL-8 (abbreviation for interleukin-8) is a CXC chemokine, while the CC chemokines include MIP-1α/β (abbreviation for macrophage inflammatory protein-1α/β), MCP-1 (abbreviation for monocyte chemoattractant protein-1), and RANTES (abbreviation for regulated upon activation, normal T-cell expressed and secreted). There also exist chemokines which do not fall into either chemokine subfamily. They are lymphotactin, which has only two cysteines and defines the C chemokine, and fractalkine that has a chemokine-like domain in the mucin structure in which the first two cysteines are separated by three amino acids and hence defines $CX_3C$ chemokine. These chemokines promote chemotaxis, cell migration, increase

the expression of cellular adhesion molecules such as integrins, and cellular adhesion, and are thought to be the protein factors intimately involved in the adhesion and infiltration of leukocytes into the pathogenic sites in such as inflammatory tissues (for references, see for example, Vaddi, K., et al., The Chemokine Facts Book, Academic Press, 1997; Chemoattractant Ligand and Their Receptors, Horuk, R., Ed., CRC Press, 1996; Ward, G.W., et al., Biochem. J., 1998, 333, 457; Luster, A.D., New Engl. J. Med., 1998, 338, 436; Baggiolini, M., Nature, 1998, 392, 565; Rollins, B.J., Blood, 1997, 90, 909; Alam, R., J. Allergy Clin. Immunol., 1997, 99, 273; Hancock, W.W., Am. J. Pathol., 1996, 148, 681; Taub, D.D., Cytokine & Growth Factor Rev., 1996, 7, 335; Strieter, R.M., et al., J. Immunol., 1996, 156, 3583; Furie, M.B., et al., Am. J. Pathol., 1995, 146, 1287; Schall, T.J., et al., Current Opinion in Immunology, 1994, 6, 865; Edginton, S.M., Biotechnology, 1993, 11, 676).

For example, MIP-1α causes a transient increase in intracellular calcium ion concentration levels and induces migration of T lymphocytes, B lymphocytes (see for example, Taub, D.D., et al., Science, 1993, 260, 355; Schall, T.J., et al., J. Exp. Med., 1993, 177, 1821), and eosinophiles (see for example, Rot, A., et al., J. Exp. Med., 1992, 176, 1489), chemotaxis of natural killer cells (see for example, Maghazachi, A.A., et al., J. Immunol., 1994, 153, 4969), expression of integrins (see for example, Vaddi, K., et al., J. Immunol., 1994, 153, 4721), and osteoclast differentiation (see for example, Kukita, T., et al., Lab. Invest., 1997, 76, 399). MIP-1α also enhances IgE and IgG4 production in B cells (see for example, Kimata, H., et al., J. Exp. Med., 1996, 183, 2397) and inhibits hematopoietic stem cell proliferation (see for example, Mayani, H., et al., Exp. Hematol., 1995, 23, 422; Keller, J.R., et al., Blood, 1994, 84, 2175; Eaves, C.J., et al., Proc. Natl. Acad. Sci. USA, 1993, 90, 12015; Bodine, D.M., et al., Blood, 1991, 78, 914; Broxmeyer, H.E., et al., Blood, 1990, 76, 1110).

With respect to the activity of MIP-1α in vivo and its role in the pathogenesis of disease, it has been reported that it is a pyrogen in rabbits (see for example Davatelis, G., et al., Science, 1989, 243, 1066); that MIP-1α injection into mouse foot pads results in an inflammatory reaction such as infiltration by neutrophils and mononuclear cells (see for example Alam, R., et al., J. Immunol., 1994, 152, 1298); that MIP-1α neutralizing antibody has an inhibitory effect or a therapeutic effect in animal models of granuloma (see for example Lukacs, N.W., et al., J. Exp. Med., 1993, 177, 1551), asthma (see for example Lukacs, N.W., et al., Eur. J. Immunol., 1995, 25, 245; Lukacs, N.W.,

et al., J. Immunol., 1997, 158, 4398), multiple sclerosis (see for example Karpus, W.J., et al., J. Immunol., 1995, 155, 5003; Karpus, W.J., et al., J. Leukoc. Biol., 1997, 62, 681), idiopathic pulmonary fibrosis (see for example Smith, R.E., et al., J. Immunol., 1994, 153, 4704; Smith, R.E., Biol. Signals, 1996, 5, 223), acute lung injury (see for example Shanley, T.P., et al., J. Immunol., 1995, 154, 4793; Standiford, T.J., et al., J. Immunol., 1995, 155, 1515), and rheumatoid arthritis (see for example Kasama, T., et al., J. Clin. Invest., 1995, 95, 2868); that coxsackie virus induced myocarditis and herpes stromal keratitis are inhibited in mice with a disrupted MIP-1α gene (see for example Cook, D.N. et al., Science, 1995, 269, 1583; Tumpey, T.M., et al., J. Virology, 1998, 72, 3705); and that significant expression of MIP-1α is observed in patients with chronic inflammatory diseases of lung (see for example Standiford, T.J., et al., J. Immunol., 1993, 151, 2852), hypersensitivity pneumonitis (see for example Denis, M., Am. J. Respir. Crit. Care Med., 1995, 151, 164), rheumatoid arthritis (see for example Koch, A.E., et al., J. Clin. Invest., 1994, 93, 921), infectious meningitis (see for example Lahrtz, F., et al., J. Neuroimmunol., 1998, 85, 33), and chronic inflammation of muscle (see for example Adams, E.M., et al., Proc. Assoc. Am. Physicians, 1997, 109, 275). These studies indicate that MIP-1α is deeply involved in the local attraction of various subtypes of leukocytes and the initiation, progression and maintenance of resulting inflammatory response.

MCP-1 (also known as MCAF (abbreviation for macrophage chemotactic and activating factor) or JE) is a CC chemokine produced by monocytes/macrophages, smooth muscle cells, fibroblasts, and vascular endothelial cells and causes cell migration and cell adhesion of monocytes (see for example Valente, A.J., et al., Biochemistry, 1988, 27, 4162; Matsushima, K., et al., J. Exp. Med., 1989, 169, 1485; Yoshimura, T., et al., J. Immunol., 1989, 142, 1956; Rollins, B.J., et al., Proc. Natl. Acad. Sci. USA, 1988, 85, 3738; Rollins, B.J., et al., Blood, 1991, 78, 1112; Jiang, Y., et al., J. Immunol., 1992, 148, 2423; Vaddi, K., et al., J. Immunol., 1994, 153, 4721), memory T lymphocytes (see for example Carr, M.W., et al., Proc. Natl. Acad. Sci. USA, 1994, 91, 3652), T lymphocytes (see for example Loetscher, P., et al., FASEB J., 1994, 8, 1055) and natural killer cells (see for example Loetscher, P., et al., J. Immunol., 1996, 156, 322; Allavena, P., et al., Eur. J. Immunol., 1994, 24, 3233), as well as mediating histamine release by basophils (see for example Alam, R., et al., J. Clin. Invest., 1992, 89, 723; Bischoff, S.C., et al., J. Exp. Med., 1992, 175, 1271; Kuna, P., et al., J. Exp. Med., 1992, 175, 489).

In addition, high expression of MCP-1 has been reported in diseases where

accumulation of monocyte/macrophage and/or T cells is thought to be important in the initiation or progression of diseases, such as atherosclerosis (see for example Hayes, I.M., et al., Arterioscler. Thromb. Vasc. Biol., 1998, 18, 397; Takeya, M., et al., Hum. Pathol., 1993, 24, 534; Yla-Herttuala, S., et al., Proc. Natl. Acad. Sci. USA, 1991, 88, 5252; Nelken, N.A., J. Clin. Invest., 1991, 88, 1121), rheumatoid arthritis (see for example Koch, A.E., et al., J. Clin. Invest., 1992, 90, 772; Akahoshi, T., et al., Arthritis Rheum., 1993, 36, 762; Robinson, E., et al., Clin. Exp. Immunol., 101, 398), nephritis (see for example Noris, M., et al., Lab. Invest., 1995, 73, 804; Wada, T., at al., Kidney Int., 1996, 49, 761; Gesualdo, L., et al., Kidney Int., 1997, 51, 155), nephropathy (see for example Saitoh, A., et al., J. Clin. Lab. Anal., 1998, 12, 1; Yokoyama, H., et al., J. Leukoc. Biol., 1998, 63, 493), pulmonary fibrosis, pulmonary sarcoidosis (see for example Sugiyama, Y., et al., Internal Medicine, 1997, 36, 856), asthma (see for example Karina, M., et al., J. Invest. Allergol. Clin. Immunol., 1997, 7, 254; Stephene, T.H., Am. J. Respir. Crit. Care Med., 1997, 156, 1377; Sousa, A.R., et al., Am. J. Respir. Cell Mol. Biol., 1994, 10, 142), multiple sclerosis (see for example McManus, C., et al., J. Neuroimmunol., 1998, 86, 20), psoriasis (see for example Gillitzer, R., et al., J. Invest. Dermatol., 1993, 101, 127), inflammatory bowel disease (see for example Grimm, M.C., et al., J. Leukoc. Biol., 1996, 59, 804; Reinecker, H.C., et al., Gastroenterology, 1995, 106, 40), myocarditis (see for example Seino, Y., et al., Cytokine, 1995, 7, 301), endometriosis (see for example Jolicoeur, C., et al., Am. J. Pathol., 1998, 152, 125), intraperitoneal adhesion (see for example Zeyneloglu, H.B., et al., Human Reproduction, 1998, 13, 1194), congestive heart failure (see for example Aurust, P., et al., Circulation, 1998, 97, 1136), chronic liver disease (see for example Marra, F., et al., Am. J. Pathol., 1998, 152, 423), viral meningitis (see for example Lahrtz, F., et al., Eur. J. Immunol., 1997, 27, 2484), Kawasaki disease (see for example Wong, M.; et al., J. Rheumatol., 1997, 24,1179) and sepsis (see for example Salkowski, C.A.; et al., Infect. Immun., 1998, 66, 3569). Furthermore, anti-MCP-1 antibody has been reported to show an inhibitory effect or a therapeutic effect in animal models of rheumatoid arthritis (see for example Schimmer, R.C., et al., J. Immunol., 1998, 160, 1466; Schrier, D.J., J. Leukoc. Biol., 1998, 63, 359; Ogata, H., et al., J. Pathol., 1997, 182, 106), multiple sclerosis (see for example Karpus, W.J., et al., J. Leukoc. Biol., 1997, 62, 681), nephritis (see for example Lloyd, C.M., et al., J. Exp. Med., 1997, 185, 1371; Wada, T., et al., FASEB J., 1996, 10, 1418), Asthma (see for example Gonzalo, J.-A., et al., J. Exp. Med., 1998, 188, 157; Lukacs, N.W., J. Immunol.,

1997, 158, 4398), atherosclerosis (see for example Guzman, L.A., et al., Circulation, 1993, 88 (suppl.), I-371), delayed type hypersensitivity (see for example Rand, M.L., et al., Am. J. Pathol., 1996, 148, 855), pulmonary hypertension (see for example Kimura, H., et al., Lab. Invest., 1998, 78, 571), and intraperitoneal adhesion (see for example Zeyneloglu, H.B., et al., Am. J. Obstet. Gynecol., 1998, 179, 438). A peptide antagonist of MCP-1, MCP-1(9-76), has been also reported to inhibit arthritis in the mouse model (see Gong, J.-H., J. Exp. Med., 1997, 186, 131), as well as studies in MCP-1-deficient mice have shown that MCP-1 is essential for monocyte recruitment in vivo (see Lu, B., et al., J. Exp. Med., 1998, 187, 601; Gu, L., et al., Moll. Cell, 1998, 2, 275).

These data indicate that chemokines such as MIP-1α and MCP-1 attract monocytes and lymphocytes to disease sites and mediate their activation and thus are thought to be intimately involved in the initiation, progression and maintenance of diseases deeply involving monocytes and lymphocytes, such as atherosclerosis, rheumatoid arthritis, psoriasis, asthma, ulcerative colitis, nephritis (nephropathy), multiple sclerosis, pulmonary fibrosis, myocarditis, hepatitis, pancreatitis, sarcoidosis, Crohn's disease, endometriosis, congestive heart failure, viral meningitis, cerebral infarction, neuropathy, Kawasaki disease, and sepsis (see for example Rovin, B.H., et al., Am. J. Kidney. Dis., 1998, 31, 1065; Lloyd, C., et al., Curr. Opin. Nephrol. Hypertens., 1998, 7, 281; Conti, P., et al., Allergy and Asthma Proc., 1998, 19, 121; Ransohoff, R.M., et al., Trends Neurosci., 1998, 21, 154; MacDermott, R.P., et al., Inflammatory Bowel Diseases, 1998, 4, 54). Therefore, drugs which inhibit the action of chemokines on target cells may be effective as a therapeutic and/or preventive drug in the diseases.

Genes encoding receptors of specific chemokines have been cloned, and it is now known that these receptors are G protein-coupled seven-transmembrane receptors present on various leukocyte populations. So far, at least five CXC chemokine receptors (CXCR1-CXCR5) and eight CC chemokine receptors (CCR1-CCR8) have been identified. For example IL-8 is a ligand for CXCR1 and CXCR2, MIP-1α is that for CCR1 and CCR5, and MCP-1 is that for CCR2A and CCR2B (for reference, see for example, Holmes, W.E., et al., Science 1991, 253, 1278-1280; Murphy P.M., et al., Science, 253, 1280-1283; Neote, K. et al., Cell, 1993, 72, 415-425; Charo, I.F., et al., Proc. Natl. Acad. Sci. USA, 1994, 91, 2752-2756; Yamagami, S., et al., Biochem. Biophys. Res. Commun., 1994, 202, 1156-1162; Combadier, C., et al., The Journal of Biological Chemistry, 1995, 270, 16491-16494, Power,

C.A., et al., J. Biol. Chem., 1995, 270, 19495-19500; Samson, M., et al., Biochemistry, 1996, 35, 3362-3367; Murphy, P.M., Annual Review of Immunology, 1994, 12, 592-633). It has been reported that lung inflammation and granuroma formation are suppressed in CCR1-deficient mice (see Gao, J.-L., et al., J. Exp. Med., 1997, 185, 1959; Gerard, C., et al., J. Clin. Invest., 1997, 100, 2022), and that recruitment of macrophages and formation of atherosclerotic lesion decreased in CCR2-deficient mice (see Boring, L., et al., Nature, 1998, 394, 894; Kuziel, W.A., et al., Proc. Natl. Acad. Sci., USA, 1997, 94, 12053; Kurihara, T., et al., J. Exp. Med., 1997, 186, 1757; Boring, L., et al., J. Clin. Invest., 1997, 100, 2552). Therefore, compound which inhibit the binding of chemokines such as MIP-1α and/or MCP-1 to these receptors, that is, chemokine receptor antagonist, may be useful as drugs which inhibit the action of chemokines such as MIP-1α and/or MCP-1 on the target cells, but there are no drugs known to have such effects.

The cyclic amine derivatives provided by the present invention is quite novel. Recently, it has been reported that the diphenylmethane derivatives (WO9724325; Hesselgesser, J., et al., J. Biol. Chem., 1998, 273, 15687), piperidine derivatives (JP9-249566), imidazobenzodiazepine derivatives (JP9-249570), benzazocine derivatives (JP9-255572), tricyclic compounds with cyclic amino group (WO9804554), phenothiazine derivatives (Bright, C., et al., Bioorg. Med. Chem. Lett., 1998, 8, 771), pieprazine derivatives (WO9744329), benzimidazole derivatives (WO9806703), distamycin analogues (Howard, O.M.Z., et al., J. Med. Chem., 1998, 41, 2184), bis-acridine derivatives (WO9830218), spiro-substituted azacycles (WO9825604; WO9825605), substituted aryl piperazines (WO9825617), aminoquinoline derivatives (WO9827815), 3-arylpiperidine derivatives (WO9831364), hexanoic amide derivatives (WO9838167), and other small molecules (WO9744329; WO9802151; WO9804554) have antagonistic activity of chemokine receptor, such as CXCR1, CXCR4, CCR1, CCR2, CCR3, and CCR5. However, these compounds differ from the compound of the present invention.

Summary of the Invention

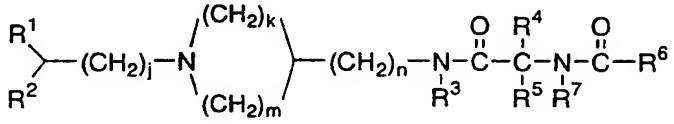
Therefore, it is an object of the present invention to provide small molecule compound which inhibits the binding of chemokines such as MIP-1α and/or MCP-1 to their receptors on the target cells.

It is another object of the present invention to establish a method to inhibit the binding to the receptors on the target cells and/or effects on target cells of chemokines such as MIP-1α and/or MCP-1.

It is an additional object of the present invention to propose a method for the treatment of diseases for which the binding of chemokines such as MIP-1α and/or MCP-1 to the receptor on the target cell is one of the causes.

As a result of intensive studies, the present inventors discovered that a cyclic amine derivative having a ureido-aryl group, its pharmaceutically acceptable $C_1$-$C_6$ alkyl addition salt or its pharmaceutically acceptable acid addition salt has an excellent activity to inhibit the binding of chemokines such as MIP-1α and/or MCP-1 and the like to the receptor of a target cell, which has led to the completion of this invention.

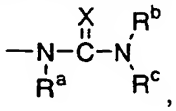
That is, the present invention is a compound of the formula (I) below:



(I)

, a pharmaceutically acceptable acid addition salt thereof or a pharmaceutically acceptable $C_1$-$C_6$ alkyl addition salt thereof (**Invention 1**),

wherein $R^1$ is a phenyl group or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, in which the phenyl or aromatic heterocyclic group may be condensed with a benzene ring or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, to form a condensed ring, and the phenyl group, aromatic heterocyclic group, or condensed ring may be substituted with one or more of a group represented by the formula:



,

a halogen atom, a hydroxy group, a cyano group, a nitro group, a carboxy group, a carbamoyl group, a $C_1$-$C_6$ alkyl group, a $C_3$-$C_8$ cycloalkyl group, a $C_2$-$C_6$ alkenyl group, a $C_1$-$C_6$ alkoxy group, a $C_1$-$C_6$ alkylthio group, a $C_2$-$C_4$ alkylenoxy group, a $C_1$-$C_3$ alkylenedioxy group, a phenyl group, a phenoxy group, a phenylthio group, a benzyl group, a benzyloxy group, a benzoylamino group, a 3-phenylureido group, a 3-phenyl-thioureido group, a $C_2$-$C_7$ alkanoyl group, a $C_2$-$C_7$ alkoxycarbonyl group, a $C_2$-$C_7$ alkanoyloxy group, a $C_2$-$C_7$ alkanoylamino group, a $C_1$-$C_6$ alkylsulfonyl group, a *N*-phenylcarbamoyl group, an amino group, a mono($C_1$-$C_6$ alkyl)amino group, or a di($C_1$-$C_6$ alkyl)amino group, wherein the substituent for the phenyl group, $C_3$-$C_8$

cycloalkyl group, aromatic heterocyclic group, or condensed ring is optionally substituted with one or more of a halogen atom, a hydroxy group, an amino group, a trifluoromethyl group, a $C_1$-$C_6$ alkyl group, or a $C_1$-$C_6$ alkoxy group;

$R^a$, $R^b$, and $R^c$ are the same or different from each other and are a hydrogen atom, a $C_1$-$C_6$ alkyl group, a carbamoyl group, or $R^b$ and $R^c$ taken together with the adjacent nitrogen atom form a pyrrolidine, a piperidine, a morpholine, a thiomoropholine, or a hexamethyleneimine;

X is a oxygen atom or a sulfur atom;

$R^2$ is a hydrogen atom or a $C_1$-$C_6$ alkyl group;

j represents an integer of 0-2;

k represents an integer of 0-2;

m represents an integer of 2-4;

n represents 0 or 1;

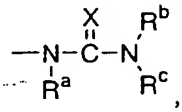
$R^3$ is a hydrogen atom or a $C_1$-$C_6$ alkyl group;

$R^4$ and $R^5$ are the same or different from each other and are a hydrogen atom, a phenyl group, or a $C_1$-$C_6$ alkyl group, in which the $C_1$-$C_6$ alkyl group is optionally substituted with one or more of a halogen atom, a hydroxy group, a cyano group, a nitro group, a carboxy group, a carbamoyl group, a mercapto group, a guanidino group, a $C_3$-$C_8$ cycloalkyl group, a $C_1$-$C_6$ alkoxy group, a $C_1$-$C_6$ alkylthio group, a phenyl group optionally substituted with one or more of a halogen atom, a hydroxy group, a $C_1$-$C_6$ alkyl group, a $C_1$-$C_6$ alkoxy group, or a benzyloxy group, a phenoxy group, a benzyloxy group, a benzyloxycarbonyl group, a $C_2$-$C_7$ alkanoyl group, a $C_2$-$C_7$ alkoxycarbonyl group, a $C_2$-$C_7$ alkanoyloxy group, a $C_2$-$C_7$ alkanoylamino group, a $C_1$-$C_6$ alkylsulfonyl group, an amino group, a mono($C_1$-$C_6$ alkyl)amino group, a di($C_1$-$C_6$ alkyl)amino group, or an aromatic heterocyclic group having 1-3 of heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof and optionally condensed with benzene ring, or $R^4$ and $R^5$ taken together form a 3 to 6 membered cyclic hydrocarbon;

$R^7$ is a hydrogen atom or a $C_1$-$C_6$ alkyl group, or $R^7$ taken together with $R^5$ represents $C_2$-$C_5$ alkylene group;

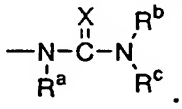
$R^6$ is a phenyl group or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, in which the phenyl or aromatic heterocyclic group may be condensed with a benzene ring or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof,

to form a condensed ring, and the phenyl group, aromatic heterocyclic group, or condensed ring may be substituted with one or more of a group represented by the formula:



a halogen atom, a hydroxy group, a mercapto group, a cyano group, a nitro group, a thiocyanato group, a carboxy group, a carbamoyl group, a trifluoromethyl group, a $C_1$-$C_6$ alkyl group, a $C_3$-$C_6$ cycloalkyl group, a $C_2$-$C_6$ alkenyl group, a $C_1$-$C_6$ alkoxy group, a $C_3$-$C_8$ cycloalkyloxy group, a $C_1$-$C_6$ alkylthio group, a $C_1$-$C_3$ alkylenedioxy group, a phenyl group, a phenoxy group, a benzyl group, a benzoyl group, a phenylsulfinyl group, a phenylsulfonyl group, a 3-phenylureido group, a 3-phenyl-thioureido group, a $C_2$-$C_7$ alkanoyl group, a $C_2$-$C_7$ alkoxycarbonyl group, a $C_2$-$C_7$ alkanoyloxy group, a $C_2$-$C_7$ alkanoylamino group, a $C_1$-$C_6$ alkylsulfonyl group, an amino group, a mono($C_1$-$C_6$ alkyl)amino group, a di($C_1$-$C_6$ alkyl)amino group, a $C_2$-$C_7$ (alkoxycarbonyl)amino group, or a $C_1$-$C_6$ (alkylsulfonyl)amino group, wherein the substituent for the phenyl group, aromatic heterocyclic group, or condensed ring is optionally substituted with one or more of a halogen atom, a cyano group, a hydroxy group, an amino group, trifluoromethyl group, a $C_1$-$C_6$ alkyl group, a $C_1$-$C_6$ alkoxy group, a $C_1$-$C_6$ alkylthio group, a mono($C_1$-$C_6$ alkyl)amino group, or a di($C_1$-$C_6$ alkyl)amino group;

provided that the phenyl group, aromatic heterocyclic group, or condensed ring in at least one of $R^1$ and $R^6$ is substituted with a 3-phenyl-thioureido group or a group represented by the formula:



Also the present invention is a method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell using a pharmaceutical preparation containing a therapeutically effective amount of a compound represented by the above formula (I), a pharmaceutically acceptable acid addition salt thereof, or a pharmaceutically acceptable $C_1$-$C_6$ alkyl addition salt thereof (**Invention 2**).

Furthermore the present invention is a method of treating a disease, in which a chemokine plays a major role, which comprises administering a pharmaceutical preparation containing a therapeutically effective amount of a compound represented by the above formula (I), a pharmaceutically acceptable

acid addition salt thereof, or a pharmaceutically acceptable $C_1$-$C_6$ alkyl addition salt thereof (Invention 3).

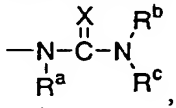
Here, the compound represented by the above formula (I) has activities to inhibit the binding of chemokines such as MIP-1α and/or MCP-1 and the like to the receptor of a target cell and activities to inhibit physiological activities of cells caused by chemokines such as MIP-1α and/or MCP-1 and the like. The compound represented by the above formula (I) is also effective as a therapeutic agent and/or preventive agent for disease such as atherosclerosis, rheumatoid arthritis, psoriasis, asthma, ulcerative colitis, nephritis (nephropathy), multiple sclerosis, pulmonary fibrosis, myocarditis, hepatitis, pancreatitis, sarcoidosis, Crohn's disease, endometriosis, congestive heart failure, viral meningitis, cerebral infarction, neuropathy, Kawasaki disease, and sepsis in which tissue infiltration of blood leukocytes plays a major role in the initiation, progression or maintenance of the disease.

---

Description of the Preferred Embodiments

(1) On Invention 1

In the above formula (I), $R^1$ is a phenyl group or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, in which the phenyl or aromatic heterocyclic group may be condensed with a benzene ring or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, to form a condensed ring, and the phenyl group, aromatic heterocyclic group, or condensed ring may be substituted with one or more of a group represented by the formula:



a halogen atom, a hydroxy group, a cyano group, a nitro group, a carboxy group, a carbamoyl group, a $C_1$-$C_6$ alkyl group, a $C_3$-$C_8$ cycloalkyl group, a $C_2$-$C_6$ alkenyl group, a $C_1$-$C_6$ alkoxy group, a $C_1$-$C_6$ alkylthio group, a $C_2$-$C_4$ alkylenoxy group, a $C_1$-$C_3$ alkylenedioxy group, a phenyl group, a phenoxy group, a phenylthio group, a benzyl group, a benzyloxy group, a benzoylamino group, a 3-phenylureido group, a 3-phenyl-thioureido group, a $C_2$-$C_7$ alkanoyl group, a $C_2$-$C_7$ alkoxycarbonyl group,

a $C_2$-$C_7$ alkanoyloxy group, a $C_2$-$C_7$ alkanoylamino group, a $C_1$-$C_6$ alkylsulfonyl group, a *N*-phenylcarbamoyl group, an amino group, a mono($C_1$-$C_6$ alkyl)amino group, or a di($C_1$-$C_6$ alkyl)amino group.

The "aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof" for $R^1$ is specifically, for example, thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazinyl, triazolyl, oxadiazolyl (furazanyl), thiadiazolyl group and the like, preferably including a thienyl, furyl, pyrrolyl, isoxazolyl, and pyridyl group.

The "condensed ring" for $R^1$ means a ring obtained by the condensation with a benzene ring or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom of a phenyl group or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom and/or a nitrogen atom, at any possible sites, suitably and specifically for example, naphthyl, indolyl, benzofuranyl, benzothienyl, quinolyl, benzimidazolyl, benzoxazolyl, benzotriazolyl, benzoxadiazolyl (benzofurazanyl), and benzothiadiazolyl group.

Among them, a phenyl group can be listed as a preferred specific example for $R^1$.

The "halogen atom" as a substituent for the phenyl group, aromatic heterocyclic group, or condensed ring in $R^1$ includes a fluorine atom, chlorine atom, bromine atom, and iodine atom, suitably including a fluorine atom, chlorine atom, and bromine atom.

The "$C_1$-$C_6$ alkyl group" as a substituent for $R^1$ means a $C_1$-$C_6$ straight-chain or a branched alkyl group such as a methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, isopropyl, isobutyl, sec-butyl, *tert*-butyl, isopentyl, neopentyl, *tert*-pentyl, isohexyl, 2-methylpentyl, 1-ethylbutyl group, and the like, suitably specifically including a methyl, ethyl, propyl, and isopropyl group.

The "$C_3$-$C_8$ cycloalkyl group" as a substituent for $R^1$ means a cyclic alkyl group such as a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl group, specifically including a cyclopropyl, cyclopentyl, and cyclohexyl group.

The "$C_2$-$C_6$ alkenyl group" as a substituent for $R^1$ means a $C_2$-$C_6$ straight-chain or a branched alkenyl group such as a vinyl, allyl, 1-propenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 4-pentenyl, 5-hexenyl, 4-methyl-3-pentenyl group, and the like, suitably specifically including a vinyl and 2-methyl-1-propenyl group.

The "$C_1$-$C_6$ alkoxy group" as a substituent for $R^1$ means group consisting of the aforementioned $C_1$-$C_6$ alkyl group and oxy group, specifically, for example, a methoxy and ethoxy group.

The "$C_1$-$C_6$ alkylthio group" as a substituent for $R^1$ means group consisting of the aforementioned $C_1$-$C_6$ alkyl group and thio group, specifically, for example, a methylthio and ethylthio group.

The "$C_2$-$C_4$ alkylenoxy group" as a substituent for $R^1$ means group consisting of a $C_2$-$C_4$ divalent alkylene group and oxy group such as a ethylenoxy ($-CH_2CH_2O-$), trimethylenoxy ($-CH_2CH_2CH_2O-$), tetramethylenoxy ($-CH_2CH_2CH_2CH_2O-$), and 1,1-dimethylethylenoxy ($-CH_2C(CH_3)_2O-$) group, specifically, for example, a ethylenoxy and trimethylenoxy group.

The "$C_1$-$C_3$ alkylenedioxy group" as a substituent for $R^1$ means group consisting of a $C_1$-$C_3$ divalent alkylene group and two oxy groups such as a methylenedioxy ($-OCH_2O-$), ethylenedioxy ($-OCH_2CH_2O-$), trimethylenedioxy ($-OCH_2CH_2CH_2O-$, and propylenedioxy ($-OCH_2CH(CH_3)O-$) group, specifically, for example, a methylenedioxy and ethylenedioxy group.

The "$C_2$-$C_7$ alkanoyl group" as a substituent for $R^1$ means $C_2$-$C_7$ straight-chain or branched alkanoyl group such as an acetyl, propanoyl, butanoyl, pentanoyl, hexanoyl, heptanoyl, isobutyryl, 3-methylbutanoyl, 2-methylbutanoyl, pivaloyl, 4-methylpentanoyl, 3,3-dimethylbutanoyl, 5-methylhexanoyl group, and the like, where the preferred and specific example includes an acetyl group.

The "$C_2$-$C_7$ alkoxycarbonyl group" as a substituent for $R^1$ means group consisting of the aforementioned $C_1$-$C_6$ alkoxy group and carbonyl group, preferably and specifically for example, a methoxycarbonyl and ethoxycarbonyl group.

The "$C_2$-$C_7$ alkanoyloxy group" as a substituent for $R^1$ means group consisting of the aforementioned $C_2$-$C_7$ alkanoyl group and oxy group, specifically, for example, an acetyloxy group.

The "$C_2$-$C_7$ alkanoylamino group" as a substituent for $R^1$ means group consisting of the aforementioned $C_2$-$C_7$ alkanoyl group and amino group, specifically, for example, an acetylamino group.

The "$C_1$-$C_6$ alkylsulfonyl group" as a substituent for $R^1$ means group

consisting of the aforementioned $C_1$-$C_6$ alkyl group and sulfonyl group, preferably and specifically, for example, a methylsulfonyl group.

The "mono($C_1$-$C_6$ alkyl)amino group" as a substituent for $R^1$ means amino group substituted with one of the aforementioned $C_1$-$C_6$ alkyl group, preferably and specifically, for example, a methylamino and ethyl amino group.

The "di($C_1$-$C_6$ alkyl)amino group" as a substituent for $R^1$ means amino group substituted with the same or different two $C_1$-$C_6$ alkyl group aforementioned, preferably and specifically, for example, a dimethylamino, diethylamino, and *N*-ethyl-*N*-methylamino group.

Among them, a halogen atom, a hydroxy group, a $C_1$-$C_6$ alkyl group, a $C_2$-$C_6$ alkenyl group, a $C_1$-$C_6$ alkoxy group, a $C_1$-$C_6$ alkylthio group, a $C_2$-$C_4$ alkylenoxy group, a methylenedioxy group, a *N*-phenylcarbamoyl group, an amino group, a mono($C_1$-$C_6$ alkyl)amino group, and a di($C_1$-$C_6$ alkyl)amino group can be listed as a preferred specific example for substituent for the phenyl group, aromatic heterocyclic group, or condensed ring in $R^1$.

Furthermore above substituent for the phenyl group, aromatic heterocyclic group, or condensed ring in $R^1$ are optionally substituted with one or more of a halogen atom, a hydroxy group, an amino group, a trifluoromethyl group, a $C_1$-$C_6$ alkyl group, or a $C_1$-$C_6$ alkoxy group. The halogen atom, $C_1$-$C_6$ alkyl group, and $C_1$-$C_6$ alkoxy group are the same as defined for the aforementioned substituents for the phenyl group, aromatic heterocyclic group, or condensed ring in $R^1$, and the same examples can be listed as preferred specific examples.

In the above formula (I), $R^a$, $R^b$, and $R^c$ are the same or different from each other and are a hydrogen atom, a $C_1$-$C_6$ alkyl group, a carbamoyl group, or $R^b$ and $R^c$ taken together with the adjacent nitrogen atom form a pyrrolidine, a piperidine, a morpholine, a thiomoropholine, or a hexamethyleneimine.

The $C_1$-$C_6$ alkyl group for $R^a$, $R^b$, and $R^c$ is the same as defined for the aforementioned substituent for the phenyl group, aromatic heterocyclic group, or condensed ring in $R^1$.

A hydrogen atom can be listed as a preferred specific example for $R^a$, and a hydrogen atom, a methyl group, ethyl group, and isopropyl group can be listed as a preferred specific example for $R^a$ and $R^b$.

In the above formula (I), X represents a oxygen atom or a sulfur atom.

In the above formula (I), $R^2$ represents a hydrogen atom or a $C_1$-$C_6$ alkyl group.

The $C_1$-$C_6$ alkyl group for $R^2$ is the same as defined for the aforementioned substituent for the phenyl group, aromatic heterocyclic group, or condensed ring in $R^1$, and the same examples can be listed as preferred specific examples.

Among them, a hydrogen atom is a preferred specific example for $R^2$.

In the above formula (I), j represents an integer of 0-2. It is particularly preferred for j to be 0.

In the above formula (I), k represents an integer of 0-2 and m represents an integer of 2-4. It is preferred to use a 2-substituted pyrrolidine in which k is 0 and m is 3, a 3-substituted pyrrolidine in which k is 1 and m is 2, a 3-substituted piperidine in which k is 1 and m is 3, a 4-substituted piperidine in which k is 2 and m is 2, or 3-substituted hexahydroazepine in which k is 1 and m is 4.

n in the above formula (I) represents 0 or 1.

Especially, 3-amidopyrrolidines in which k is 1, m is 2, and n is 0 and 4-(amidomethyl)piperidines in which k is 2 , m is 2, and n is 1 can be listed as a particularly preferred example.

$R^3$ in the above formula (I) represents a hydrogen atom or a $C_1$-$C_6$ alkyl group.

The $C_1$-$C_6$ alkyl group for $R^3$ is the same as defined for the aforementioned substituent for the phenyl group, aromatic heterocyclic group, or condensed ring in $R^1$, and the same examples can be listed as preferred specific examples.

Among them, a hydrogen atom is a preferred specific example for $R^3$.

In the above formula (I), $R^4$ and $R^5$ are the same or different from each other and are a hydrogen atom, a hydroxy group, a phenyl group, or a $C_1$-$C_6$ alkyl group, in which the $C_1$-$C_6$ alkyl group is optionally substituted with one or more of a halogen atom, a hydroxy group, a cyano group, a nitro group, a carboxy group, a carbamoyl group, a mercapto group, a guanidino group, a $C_3$-$C_8$ cycloalkyl group, a $C_1$-$C_6$ alkoxy group, a $C_1$-$C_6$ alkylthio group, a phenyl group optionally substituted with one or more of a halogen atom, a hydroxy group, a $C_1$-$C_6$ alkyl group, a $C_1$-$C_6$ alkoxy group, or a benzyloxy group, a phenoxy group, a benzyloxy

group, a benzyloxycarbonyl group, a $C_2$-$C_7$ alkanoyl group, a $C_2$-$C_7$ alkoxycarbonyl group, a $C_2$-$C_7$ alkanoyloxy group, a $C_2$-$C_7$ alkanoylamino group, a $C_1$-$C_6$ alkylsulfonyl group, an amino group, a mono($C_1$-$C_6$ alkyl)amino group, a di($C_1$-$C_6$ alkyl)amino group, or an aromatic heterocyclic group having 1-3 of heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof and optionally condensed with benzene ring, or $R^4$ and $R^5$ taken together form a 3 to 6 membered cyclic hydrocarbon.

The $C_1$-$C_6$ alkyl group for $R^4$ and $R^5$ is the same as defined for the aforementioned substituent for the phenyl group, aromatic heterocyclic group, or condensed ring in $R^1$, and the same examples can be listed as preferred specific examples.

The halogen atom, $C_3$-$C_8$ cycloalkyl group, $C_1$-$C_6$ alkoxy group, $C_1$-$C_6$ alkylthio group, $C_2$-$C_7$ alkanoyl group, $C_2$-$C_7$ alkoxycarbonyl group, $C_2$-$C_7$ alkanoyloxy group, $C_2$-$C_7$ alkanoylamino group, $C_1$-$C_6$ alkylsulfonyl group, mono($C_1$-$C_6$ alkyl)amino group, and di($C_1$-$C_6$ alkyl)amino group as a substituent for the $C_1$-$C_6$ alkyl group in $R^4$ and $R^5$ are the same as defined for the aforementioned substituent for the phenyl group, aromatic heterocyclic group, or condensed ring in $R^1$, and the same examples can be listed as preferred specific examples.

The aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof as substituent for the $C_1$-$C_6$ alkyl group in $R^4$ and $R^5$ is the same as defined for the aforementioned group for $R^1$, and the same examples can be listed as preferred specific examples.

The halogen atom, $C_1$-$C_6$ alkyl group, and $C_1$-$C_6$ alkoxy group for the substituent for the phenyl group which is substituent for the $C_1$-$C_6$ alkyl group in $R^4$ and $R^5$ are the same as defined for the aforementioned substituent for the phenyl group, aromatic heterocyclic group, or condensed ring in $R^1$, and the same examples can be listed as preferred specific examples.

The "3 to 6 membered cyclic hydrocarbon" consisting of $R^4$, $R^5$, and the adjacent carbon atom includes a cyclopropane, cyclobutane, cyclopentane, and cyclohexane.

Among them, a hydrogen atom can be listed as a preferred specific example for $R^4$ and $R^5$.

In the above formula (I), $R^7$ is a hydrogen atom or a $C_1$-$C_6$ alkyl group, or $R^7$ taken together with $R^5$ represents a $C_2$-$C_5$ alkylene group.

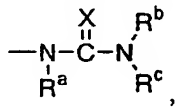
The $C_1$-$C_6$ alkyl group for $R^7$ are the same as defined for the aforementioned

substituent for the phenyl group, aromatic heterocyclic group, or condensed ring in $R^1$, and the same examples can be listed as preferred specific examples.

The "$C_2$-$C_5$ alkylene group" consisting of $R^5$ and $R^7$ means $C_2$-$C_5$ straight-chain or branched alkylene group such as a methylene, ethylene, propylene, trimethylene, tetramethylene, 1-methyltrimethylene, pentamethylene group, and the like, suitably and specifically including a ethylene, trimethylene and tetramethylene group.

A hydrogen atom is a preferred specific example for $R^7$.

In the above formula (I), $R^6$ is a phenyl group or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, in which the phenyl or aromatic heterocyclic group may be condensed with a benzene ring or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, to form a condensed ring, and the phenyl group, aromatic heterocyclic group, or condensed ring may be substituted with one or more of a group represented by the formula:



a halogen atom, a hydroxy group, a mercapto group, a cyano group, a nitro group, a thiocyanato group, a carboxy group, a carbamoyl group, a trifluoromethyl group, a $C_1$-$C_6$ alkyl group, a $C_3$-$C_6$ cycloalkyl group, a $C_2$-$C_6$ alkenyl group, a $C_1$-$C_6$ alkoxy group, a $C_3$-$C_8$ cycloalkyloxy group, a $C_1$-$C_6$ alkylthio group, a $C_1$-$C_3$ alkylenedioxy group, a phenyl group, a phenoxy group, a benzyl group, a benzoyl group, a phenylsulfinyl group, a phenylsulfonyl group, a 3-phenylureido group, a 3-phenyl-thioureido group, a $C_2$-$C_7$ alkanoyl group, a $C_2$-$C_7$ alkoxycarbonyl group, a $C_2$-$C_7$ alkanoyloxy group, a $C_2$-$C_7$ alkanoylamino group, a $C_1$-$C_6$ alkylsulfonyl group, an amino group, a mono($C_1$-$C_6$ alkyl)amino group, a di($C_1$-$C_6$ alkyl)amino group, a $C_2$-$C_7$ (alkoxycarbonyl)amino group, or a $C_1$-$C_6$ (alkylsulfonyl)amino group.

The aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, and the condensed ring for $R^6$ is the same as defined for the aforementioned $R^1$, and the same examples can be listed as preferred specific examples.

Among them, a phenyl group can be listed as a preferred specific example for $R^6$.

The halogen atom, $C_1$-$C_6$ alkyl group, $C_3$-$C_6$ cycloalkyl group, $C_2$-$C_6$ alkenyl group, $C_1$-$C_6$ alkoxy group, $C_1$-$C_6$ alkylthio group, $C_1$-$C_3$ alkylenedioxy group, $C_2$-$C_7$ alkanoyl group, $C_2$-$C_7$ alkoxycarbonyl group, $C_2$-$C_7$ alkanoyloxy group, $C_2$-$C_7$ alkanoylamino group, $C_1$-$C_6$ alkylsulfonyl group, mono($C_1$-$C_6$ alkyl)amino group, and di($C_1$-$C_6$ alkyl)amino group as a substituent for the phenyl group, aromatic heterocyclic group, or condensed ring in $R^6$ are the same as defined for the aforementioned substituent for the phenyl group, aromatic heterocyclic group, or condensed ring in $R^1$, and the same examples can be listed as preferred specific examples.

The "$C_3$-$C_8$ cycloalkyloxy group" as a substituent for $R^6$ means group consisting of the aforementioned $C_3$-$C_8$ cycloalkyl group and oxy group, specifically, for example, a cyclopropyloxy, cyclopentyloxy, and cyclohexyloxy group.

The "$C_2$-$C_7$ (alkoxycarbonyl)amino group" as a substituent for $R^6$ means group consisting of the aforementioned $C_2$-$C_7$ alkoxycarbonyl group and amino group, specifically, for example, a (methoxycarbonyl)amino and (ethoxycarbonyl)amino group.

The "$C_1$-$C_6$ (alkylsulfonyl)amino" group as a substituent for $R^6$ means group consisting of the aforementioned $C_1$-$C_6$ alkylsulfonyl group and amino group, specifically, for example, a (methylsulfonyl)amino group.

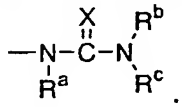
Among them, a halogen atom, a mercapto group, a nitro group, a thiocyanato group, a trifluoromethyl group, a $C_1$-$C_6$ alkyl group, a $C_1$-$C_6$ alkoxy group, a phenyl group, a phenylsulfonyl group, a $C_2$-$C_7$ alkanoylamino group, an amino group, or a trifluoromethoxy group can be listed as preferred specific example for substituent for the phenyl group, aromatic heterocyclic group, or condensed ring in $R^6$.

Furthermore above substituents for the phenyl group, aromatic heterocyclic group, or condensed ring in $R^6$ are optionally substituted with one or more of a halogen atom, a cyano group, a hydroxy group, an amino group, trifluoromethyl group, a $C_1$-$C_6$ alkyl group, a $C_1$-$C_6$ alkoxy group, a $C_1$-$C_6$ alkylthio group, a mono($C_1$-$C_6$ alkyl)amino group, or a di($C_1$-$C_6$ alkyl)amino group.

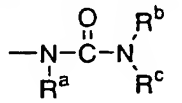
The halogen atom, $C_1$-$C_6$ alkyl group, $C_1$-$C_6$ alkoxy group, a $C_1$-$C_6$ alkylthio group, mono($C_1$-$C_6$ alkyl)amino group, and di($C_1$-$C_6$ alkyl)amino group are the same

as defined for the aforementioned substituents for the phenyl group, aromatic heterocyclic group, or condensed ring in $R^1$, and the same examples can be listed as preferred specific examples.

In the above formula (I), the phenyl group, aromatic heterocyclic group, or condensed ring in at least one of $R^1$ and $R^6$ is substituted with a 3-phenyl-thioureido group or a group represented by the formula:



In other words, the compound represented by the formula (I) of the present invention always has one or more of a 3-phenyl-thioureido group or a group represented by the formula:



on the phenyl group, aromatic heterocyclic group, or condensed ring in $R^1$ and/or $R^6$.

(2) On Invention 2 and 3

The compound represented by the formula (I) above, a pharmaceutically acceptable acid addition salt thereof or a pharmaceutically acceptable $C_1$-$C_6$ alkyl addition salt can be used to prepare a chemokine receptor antagonist preparation of the present invention by formulating the therapeutically effected amount and a carrier and/or diluent into a pharmaceutical composition. Thus, the ureido-substituted cyclic amine derivatives shown by the above formula (I), a pharmaceutically acceptable acid addition salt thereof or a pharmaceutically acceptable $C_1$-$C_6$ alkyl addition salt can be administered orally or by parenterally, for example, intravenously, subcutaneously, intramuscularly, percutaneously or intrarectally.

The oral administration can be accomplished in the form of tablets, pills, granules, powder, solution, suspension, capsules, etc.

The tablets for example can be prepared using a vehicle such as lactose, starch and crystallized cellulose; binder such as carboxymethylcellulose, methylcellulose, and polyvinylpyrrolidone; disintegrator such as sodium alginate, sodium bicarbonate and sodium lauryl sulfate, etc.

Pills, powder and granule preparations can be prepared by a standard method using the vehicles mentioned above. Solution or suspension can be prepared by a standard method using glycerin ester such as tricaprylin and triacetin or alcohols such as ethanol. Capsules can be made by charging granules, powder or solution in gelatin, etc.

Subcutaneous, intramuscular or intravenous preparations can be prepared as an injection using aqueous or nonaqueous solution. Aqueous solution for example may include isotonic sodium chloride solution. Nonaqueous solutions may include for example, propyleneglycol, polyethyleneglycol, olive oil, ethyl oleate, etc., and optionally, one can add antiseptics and stabilizers. For injection, one can be sterilized by filtration through a bacterial filter or combination of disinfectant.

Percutaneous administration may be in the form of an ointment or cream, and ointment can be prepared in the standard manner using fatty oils such as castor oil and olive oil, or Vaseline, while creams can be made using fatty oils or emulsifying agent such as diethyleneglycol and sorbitan esters of fatty acid.

For intrarectal administration, one can use standard suppositories using gelatin soft capsules, etc.

The ureido-substituted cyclic amine derivatives of the present invention, a pharmaceutically acceptable acid addition salt thereof or a pharmaceutically acceptable $C_1$-$C_6$ alkyl addition salt is administered at a dose that varies depending on the type of disease, route of administration, age and sex of patient, and severity of disease, but is likely to be 1-500 mg/day in an average adult.

(3) Matter common throughout Invention 1, 2 and 3

Preferred specific examples for the ureido-substituted cyclic amine compound in the above formula (I) includes:

(3*R*)-1-(4-chlorobenzyl)-3-[{*N*-(2-(3-methylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-chlorobenzyl)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-chlorobenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-

(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-ethylbenzyl)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-ethylbenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]-1-(3,4-methylenedioxybenzyl)pyrrolidine;

(3*R*)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]-1-(3,4-methylenedioxybenzyl)pyrrolidine;

(3*R*)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]-1-(3-hydroxy-4-methoxybenzyl)-pyrrolidine;

(3*R*)-1-(3-hydroxy-4-methoxybenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]-1-(4-hydroxy-3-methoxybenzyl)-pyrrolidine;

(3*R*)-1-(4-hydroxy-3-methoxybenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(2,3-dihydrobenzofuran-5-ylmethyl)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(2,3-dihydrobenzofuran-5-ylmethyl)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]-1-(4-methoxybenzyl)pyrrolidine;

(3*R*)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]-1-(4-methoxybenzyl)pyrrolidine;

(3*R*)-1-(3-amino-4-methylbenzyl)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(3-amino-4-methylbenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(3-amino-4-methoxybenzyl)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(3-amino-4-methoxybenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-dimethylaminobenzyl)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-dimethylaminobenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(3-amino-4-chlorobenzyl)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(3-amino-4-chlorobenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(3-amino-4-hydroxybenzyl)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(3-amino-4-hydroxybenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(2-amino-4-chlorobenzyl)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(2-amino-4-chlorobenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-chlorobenzyl)-3-[{*N*-(2-(3,3-dimethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-chlorobenzyl)-3-[{*N*-(5-trifluoromethyl-2-(1,3,3-trimethylureido)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-chlorobenzyl)-3-[{*N*-(2-(1-methylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-chlorobenzyl)-3-[{*N*-(2-(3-methylthioureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-chlorobenzyl)-3-[{*N*-(5-trifluoromethoxy-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-chlorobenzyl)-3-[{*N*-(5-chloro-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-chlorobenzyl)-3-[{*N*-(5-bromo-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-chlorobenzyl)-3-[{*N*-(5-nitro-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-chlorobenzyl)-3-[{*N*-(5-iodo-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

1-(4-chlorobenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-chlorobenzyl)-3-[{*N*-(5-trifluoromethyl-2-

ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-chlorobenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(2-methyl-4,5-methylenedioxybenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-methoxy-2-methylbenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-ethyl-2-methylbenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(3-hydroxy-4-methoxybenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-hydroxy-3-methoxybenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(2,3-dihydrobenzofuran-5-ylmethyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-ethylbenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(3,4-methylenedioxybenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-methoxybenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(3-amino-4-methylbenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(3-amino-4-methoxybenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-dimethylaminobenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(3-amino-4-chlorobenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(3-amino-4-hydroxybenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(2-amino-4-chlorobenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-methylthiobenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-vinylbenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-propylbenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-methylbenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(2,4-dimethylbenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-isopropylbenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-hydroxybenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-pyridylmethyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(3,5-dimethylisoxazol-4-ylmethyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-bromobenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chloro-2-ureidobenzyl)pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-chloro-2-(3-ethylureido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-chloro-2-(3-isopropylureido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{2-(1-carbamoylureido)-4-chlorobenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chloro-3-ureidobenzyl)pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-chloro-3-(3-ethylureido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-chloro-3-(3-isopropylureido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1-carbamoylureido)-4-chlorobenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-chloro-3-(3-phenyl-thioureido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-methyl-3-ureidobenzyl)pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-

ethylureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-isopropylureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1-carbamoylureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1,1-dimethylureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1,1-diethylureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(1-pyrrolidinecarboxamido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(1-piperidinecarboxamido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(4-morpholinecarboxamido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(4-thiomorpholinecarboxamido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(3-methyl-thioureido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-ethyl-thioureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-isopropyl-thioureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(3-phenyl-thioureido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-(4-methyl-3-ureidobenzyl)pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{3-(3-ethylureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{3-(3-isopropylureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{3-(1-carbamoylureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{3-(1,1-dimethylureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{3-(1,1-diethylureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{4-methyl-3-(1-pyrrolidinecarboxamido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{4-methyl-3-(1-piperidinecarboxamido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{4-methyl-3-(4-morpholinecarboxamido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{4-methyl-3-(4-thiomorpholinecarboxamido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{4-methyl-3-(3-methyl-thioureido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{3-(3-ethyl-thioureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{3-(3-isopropyl-thioureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{4-methyl-3-(3-phenyl-thioureido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-methoxy-3-ureidobenzyl)pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-ethylureido)-4-methoxybenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-isopropylureido)-4-methoxybenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1-carbamoylureido)-4-methoxybenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-hydroxy-3-ureidobenzyl)pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-ethylureido)-4-hydroxybenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-hydroxy-3-(3-isopropylureido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1-carbamoylureido)-4-hydroxybenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1,1-dimethylureido)-4-hydroxylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1,1-diethylureido)-4-hydroxybenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-

hydroxy-3-(1-pyrrolidinecarboxamido)benzyl}pyrrolidine;

(3*S*)-1-(4-chlorobenzyl)-3-[{*N*-(2-(3-methylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-chlorobenzyl)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-chlorobenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-ethylbenzyl)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-ethylbenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*S*)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]-1-(3,4-methylenedioxybenzyl)pyrrolidine;

(3*S*)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]-1-(3,4-methylenedioxybenzyl)pyrrolidine;

(3*S*)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]-1-(3-hydroxy-4-methoxybenzyl)-pyrrolidine;

(3*S*)-1-(3-hydroxy-4-methoxybenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*S*)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]-1-(4-hydroxy-3-methoxybenzyl)-pyrrolidine;

(3*S*)-1-(4-hydroxy-3-methoxybenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(2,3-dihydrobenzofuran-5-ylmethyl)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(2,3-dihydrobenzofuran-5-ylmethyl)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*S*)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]-1-(4-methoxybenzyl)pyrrolidine;

(3*S*)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]-1-(4-methoxybenzyl)pyrrolidine;

(3*S*)-1-(3-amino-4-methylbenzyl)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(3-amino-4-methylbenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(3-amino-4-methoxybenzyl)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(3-amino-4-methoxybenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-dimethylaminobenzyl)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-dimethylaminobenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(3-amino-4-chlorobenzyl)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(3-amino-4-chlorobenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(3-amino-4-hydroxybenzyl)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(3-amino-4-hydroxybenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(2-amino-4-chlorobenzyl)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(2-amino-4-chlorobenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-chlorobenzyl)-3-[{*N*-(2-(3,3-dimethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-chlorobenzyl)-3-[{*N*-(5-trifluoromethyl-2-(1,3,3-trimethylureido)benzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-chlorobenzyl)-3-[{*N*-(2-(1-methylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-chlorobenzyl)-3-[{*N*-(2-(3-methylthioureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-chlorobenzyl)-3-[{*N*-(5-trifluoromethoxy-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-chlorobenzyl)-3-[{*N*-(5-chloro-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-chlorobenzyl)-3-[{*N*-(5-bromo-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-chlorobenzyl)-3-[{*N*-(5-nitro-2-

ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-chlorobenzyl)-3-[{*N*-(5-iodo-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-chlorobenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(2-methyl-4,5-methylenedioxybenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-methoxy-2-methylbenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-ethyl-2-methylbenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(3-hydroxy-4-methoxybenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-hydroxy-3-methoxybenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(2,3-dihydrobenzofuran-5-ylmethyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-ethylbenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(3,4-methylenedioxybenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-methoxybenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(3-amino-4-methylbenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(3-amino-4-methoxybenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-dimethylaminobenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(3-amino-4-chlorobenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(3-amino-4-hydroxybenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(2-amino-4-chlorobenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-methylthiobenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-vinylbenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-propylbenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-methylbenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(2,4-dimethylbenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-isopropylbenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-hydroxybenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-pyridylmethyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(3,5-dimethylisoxazol-4-ylmethyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-1-(4-bromobenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chloro-2-ureidobenzyl)pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-chloro-2-(3-ethylureido)benzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-chloro-2-(3-isopropylureido)benzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{2-(1-carbamoylureido)-4-chlorobenzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chloro-3-ureidobenzyl)pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-chloro-3-(3-ethylureido)benzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-chloro-3-(3-isopropylureido)benzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1-carbamoylureido)-4-chlorobenzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-chloro-3-(3-phenyl-thioureido)benzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-

methyl-3-ureidobenzyl)pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-ethylureido)-4-methylbenzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-isopropylureido)-4-methylbenzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1-carbamoylureido)-4-methylbenzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1,1-dimethylureido)-4-methylbenzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1,1-diethylureido)-4-methylbenzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(1-pyrrolidinecarboxamido)benzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(1-piperidinecarboxamido)benzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(4-morpholinecarboxamido)benzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(4-thiomorpholinecarboxamido)benzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(3-methyl-thioureido)benzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-ethyl-thioureido)-4-methylbenzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-isopropyl-thioureido)-4-methylbenzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(3-phenyl-thioureido)benzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-(4-methyl-3-ureidobenzyl)pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{3-(3-ethylureido)-4-methylbenzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{3-(3-isopropylureido)-4-methylbenzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{3-(1-carbamoylureido)-4-methylbenzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{3-(1,1-dimethylureido)-4-methylbenzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{3-(1,1-diethylureido)-4-methylbenzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{4-methyl-3-(1-pyrrolidinecarboxamido)benzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{4-methyl-3-(1-piperidinecarboxamido)benzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{4-methyl-3-(4-morpholinecarboxamido)benzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{4-methyl-3-(4-thiomorpholinecarboxamido)benzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{4-methyl-3-(3-methyl-thioureido)benzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{3-(3-ethyl-thioureido)-4-methylbenzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{3-(3-isopropyl-thioureido)-4-methylbenzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{4-methyl-3-(3-phenyl-thioureido)benzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-methoxy-3-ureidobenzyl)pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-ethylureido)-4-methoxybenzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-isopropylureido)-4-methoxybenzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1-carbamoylureido)-4-methoxybenzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-hydroxy-3-ureidobenzyl)pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-ethylureido)-4-hydroxybenzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-hydroxy-3-(3-isopropylureido)benzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1-carbamoylureido)-4-hydroxybenzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1,1-dimethylureido)-4-hydroxylbenzyl}pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-

(1,1-diethylureido)-4-hydroxybenzyl)pyrrolidine;

(3*S*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-hydroxy-3-(1-pyrrolidinecarboxamido)benzyl}pyrrolidine;

1-(4-chlorobenzyl)-4-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}aminomethyl]piperidine;

1-(4-chlorobenzyl)-4-[{*N*-(4,5-difluoro-2-ureidobenzoyl)glycyl}aminomethyl]piperidine;

4-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}aminomethyl]-1-(4-chloro-2-ureidobenzyl)piperidine;

4-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}aminomethyl]-1-(4-chloro-3-ureidobenzyl)piperidine;

4-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}aminomethyl]-1-(4-methyl-3-ureidobenzyl)piperidine;

4-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}aminomethyl]-1-(4-methoxy-3-ureidobenzyl)piperidine; and

4-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}aminomethyl]-1-(4-hydroxy-3-ureidobenzyl)piperidine.

The present invention can also use acid addition salt of the cyclic amine compound substituted with ureido group where such acids include, for example, mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, carbonic acid, and the like, as well as organic acids such as maleic acid, citric acid, malic acid, tartaric acid, fumaric acid, methanesulfonic acid, trifluoroacetic acid, formic acid, and the like.

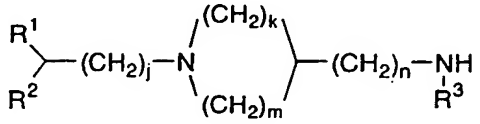
Furthermore, the present invention can also use a $C_1$-$C_6$ alkyl addition salt of the cyclic amine compound, such as 1-(4-chlorobenzyl)-1-methyl-4-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}aminomethyl]piperidinium iodide, where such alkyl include, for example, a methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, *tert*-pentyl, 2-methylpentyl, 1-ethylbutyl, and the like, suitably specifically including, a methyl and ethyl group. As preferred specific examples for counter anion of the ammonium cation, a halide anion such as fluoride, chloride, bromide or iodide can be listed.

The present invention may use racemates and all possible optically active forms of the compound represented by the above formula (I).

Compound represented by the above general formula (I) can be synthesized by any of the general preparations given below.

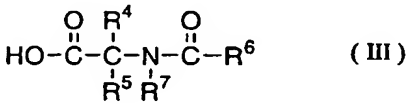
(Preparation 1)

A preparation which call for treating one equivalent of a compound represented by the formula (II) below:



(II)

{where $R^1$, $R^2$, $R^3$, j, k, m, and n are the same as defined respectively in the above formula (I)} with 0.1-10 equivalents of a carboxylic acid represented by the formula (III) below:



(III)

{where $R^4$, $R^5$, $R^6$, and $R^7$ are the same as defined respectively in the above formula (I)}, or its reactive derivative, either in the absence or presence of solvent.

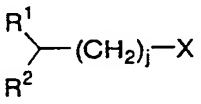
The reactive derivative for the carboxylic acid in the above formula (III) include highly reactive carboxylic acid derivatives, which are usually used in synthetic organic chemistry, such as acid halides, acid anhydrides, mixed acid anhydrides.

Such reactions can be more smoothly run by using suitable amounts of a dehydrating agent such as molecular sieve, coupling reagent such as dicyclohexylcarbodiimide (DCC), *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide (EDCI or WSC), carbonyldiimidazole (CDI), *N*-hydroxysuccinimide (HOSu), *N*-hydroxybenzotriazole (HOBt), benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP®), 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), 2-(5-norbornene-2,3-dicarboxyimido)-1,1,3,3-tetramethyluronium tetrafluoroborate (TNTU), *O*-(*N*-succinimidyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TSTU), bromotris(pyrrolidino)phosphonium hexafluorophosphate (PyBroP®), and the like, or base including inorganic salts such as potassium

carbonate, sodium carbonate, sodium hydrogencarbonate, and the like, amines such as triethylamine, diisopropylethylamine, and pyridine, and the like, or polymer supported bases such as (piperidinomethyl)polystyrene, (morpholinomethyl)polystyrene, (diethylaminomethyl)polystyrene, poly(4-vinylpyridine), and the like.

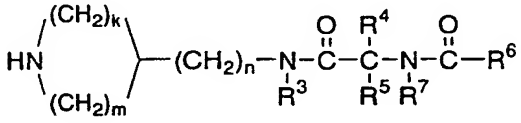
(Preparation 2)

A preparation which calls for treating 1 equivalent of an alkylating reagent given by the formula (IV) below:



(IV)

{where $R^1$, $R^2$, and j are the same as defined respectively in the above formula (I)}; X represents a halogen atom, alkylsulfonyloxy group, or arylsulfonyloxy group}, with 0.1-10 equivalents of a compound represented by the formula (V) below:



(V)

{where $R^3$, $R^4$, $R^5$, $R^6$, $R^7$, k, m, and n are the same as defined respectively in the above formula (I)} either in the absence or presence of solvent.

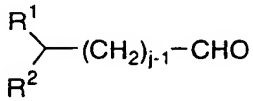
Such reactions can be more smoothly run if a base similar to that used in the above preparation 1 is present. In addition, the reactions in these preparations can also be promoted by iodide such as potassium iodide, sodium iodide, and the like.

In the above formula (IV), X represents a halogen atom, alkylsulfonyloxy group, arylsulfonyloxy group. Such halogen atoms include preferably chlorine, bromine, and iodine atoms. Suitable specific examples for the alkylsulfonyloxy groups include methylsulfonyloxy, trifluoromethylsulfonyloxy group, and the like. A preferred specific example for the arylsulfonyloxy group includes a tosyloxy group.

(Preparation 3)

A preparation which calls for treating 1 equivalent of an aldehyde

represented by the formula (VI) below:



(VI)

{where $R^1$ and $R^2$ are the same as defined respectively in the above formula (I); j represents 1 or 2} or the formula (VII) below:

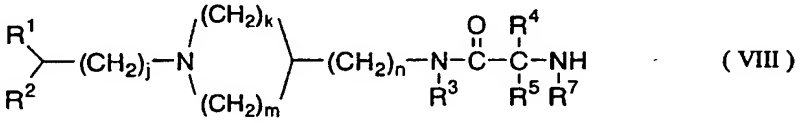
(VII)

{where $R^1$ is the same as defined in the above formula (I); j represents 0}, with 0.1-10 equivalents of a compound represented by the formula (V) either in the absence or presence of solvent under reductive conditions.

Such reactions are in general called reductive amination reactions and such reductive conditions may be generated by catalytic hydrogenation using a catalyst containing a metal such as palladium, platinum, nickel, rhodium, or the like, using complex hydrides, such as lithium aluminum hydride, sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, and the like, boranes, or electrolytic reduction, and the like.

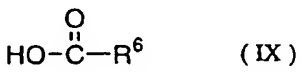
(Preparation 4)

A preparation which call for treating one equivalent of a compound represented by the formula (VIII) below:



(VIII)

{where $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $R^7$, j, k, m, and n are the same as defined respectively in the above formula (I)} with 0.1-10 equivalents of a carboxylic acid represented by the formula (IX) below:



(IX)

{where $R^6$ is the same as defined in the above formula (I)}, or its reactive derivative, either in the absence or presence of solvent.

The reactive derivative for the carboxylic acid in the above formula (IX) include highly reactive carboxylic acid derivative, which are usually used in synthetic organic chemistry, such as acid halides, acid anhydrides, mixed acid anhydrides.

Such reactions can be more smoothly run by using suitable amounts of a dehydrating agent, coupling reagent, or base which are similar to those used in the above preparation 1.

The arylurea moiety of the ureido-substituted cyclic amine derivative of the present invention is generally derived from the corresponding arylamine with the known method using sodium cyanate, sodium thiocyanate, trimethylsilyl isocyanate, alkyl isocaynate, alkyl isothiocyanate, and the like or *N,N*-dialkylcarbonyl halide such as N,N-dimethylcarbamoyl chloride, 1-pyrrolidinecarbonyl chloride, and the like. The arylurea derivatives can be also synthesized by conversion of arylamine into aryl isocyanate or aryl isothiocyanate followed by reaction with the corresponding amine. These methods to synthesize urea derivatives are well known in synthetic organic chemistry.

If the substrates submitted to each of the above preparations contains a substituent which reacts under each reaction condition or is thought to adversely affect the reaction in general in synthetic organic chemistry, that functional group can be protected by a known suitable protecting group followed by the reaction of the above preparations and deprotection using a known procedure to obtain the desired compound.

Furthermore, a compound of the present invention can be prepared by the further conversion of the substituent(s) of the compound, prepared with the above preparations 1-4, using known reactions which are usually used in synthetic organic chemistry, such as alkylation, acylation, reduction, and so on.

Each of the above preparations may use solvents for the reaction such as halogenated hydrocarbons such as dichloromethane, chloroform, and the like, aromatic hydrocarbons such as benzene, toluene, and the like, ethers such as diethyl ether, tetrahydrofuran, and the like, esters such as ethyl acetate, aprotic polar solvents such as dimethylformamide, dimethyl sulfoxide, acetonitrile, and the like, alcohols such as methanol, ethanol, isopropyl alcohol, and the like.

The reaction temperature in either of the preparations should be in the range of -78 °C - +150 °C, preferably 0 °C - 100 °C. After completion of the

reaction, the usual isolation and purification operations such as concentration, filtration, extraction, solid-phase extraction, recrystallization, chromatography, and the like may be used, to isolate the desired compound represented by the above formula (I). These can be converted into pharmaceutically acceptable acid addition salt or $C_1$-$C_6$ alkyl addition salt by the usual method.

Potential Industrial Utilities

The chemokine receptor antagonist, which contain the cyclic amine compound possessing ureido group, its pharmaceutically acceptable acid addition salt or a pharmaceutically acceptable $C_1$-$C_6$ alkyl addition salt of this invention, which inhibits chemokines such as MIP-1α and/or MCP-1 and the like from action on target cells, are useful as therapeutic agents and/or preventive preparation for diseases such as atherosclerosis, rheumatoid arthritis, psoriasis, asthma, ulcerative colitis, nephritis (nephropathy), multiple sclerosis, pulmonary fibrosis, myocarditis, hepatitis, pancreatitis, sarcoidosis, Crohn's disease, endometriosis, congestive heart failure, viral meningitis, cerebral infarction, neuropathy, Kawasaki disease, sepsis, and the like, in which tissue infiltration of blood monocytes, lymphocytes, and the like plays a major role in the initiation, progression, and maintenance of the disease.

Examples

The present invention is now specifically described by the following examples. However, the present invention is not limited to these compounds described in these examples.

**Reference Example 1: Preparation of 3-Amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride.**

4-Chlorobenzyl chloride (4.15 g, 25.8 mmol) and $^{i}Pr_2NEt$ (6.67 g, 51.6 mmol) were added to a solution of 3-{(*tert*-butoxycarbonyl)amino}pyrrolidine (4.81 g, 25.8 mmol) in DMF (50 mL). The reaction mixture was stirred at 70 °C for 15 h and the solvent was removed under reduced pressure. Recrystallization ($CH_3CN$, 50 mL) provided 3-(*tert*-butoxycarbonyl)amino-1-(4-chlorobenzyl)pyrrolidine as a pale yellow solid (6.43 g, 80.2%): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.37 (s, 9 H), 1.5-1.7 (br, 1 H), 2.1-2.4 (m, 2 H), 2.5-2.7 (m, 2 H), 2.83 (br, 1 H), 3.57 (s, 2 H), 4.1-4.3 (br, 1 H), 4.9-5.1 (br, 1 H), 7.15-7.35 (br, 4 H); The purity was determined by RPLC/MS (98%); ESI/MS m/e 311.0 ($M^+$+H, $C_{16}H_{24}ClN_2O_2$).

A solution of 3-(*tert*-butoxycarbonyl)amino-1-(4-chlorobenzyl)pyrrolidine (6.38 g, 20.5 mmol) in $CH_3OH$ (80 mL) was treated with 1 N HCl-$Et_2O$ (100 mL) and was stirred at 25 °C for 15 h. The solvent was removed under reduced pressure to afford a solid which was purified by recrystallization (1:2 $CH_3OH$-$CH_3CN$, 150 mL) to give 3-amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride as a white powder (4.94 g, 85%): $^1$H NMR ($d_6$-DMSO, 300 MHz) $\delta$ 3.15 (br, 1 H), 3.3-3.75 (br-m, 4 H), 3.9 (br, 1 H), 4.05 (br, 1 H), 4.44 (br, 1 H), 4.54 (br, 1 H), 7.5-7.7 (m, 4 H), 8.45 (br, 1 H), 8.60 (br, 1 H); The purity was determined by RPLC/MS (>99%); ESI/MS m/e 211.0 ($M^+$+H, $C_{11}H_{16}ClN_2$).

Optically active (*R*)-3-amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride and (*S*)-3-amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride were also prepared pursuant to the above method using the corresponding reactant respectively. The products showed the same $^1$H NMR with that of the racemate.

**Reference Example 2: Preparation of (*R*)-3-{*N*-(*tert*-Butoxycarbonyl)glycyl}amino-1-(4-chlorobenzyl)pyrrolidine.**

A mixture of (*R*)-3-amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride (4.54 g, 16.0 mmol), 2 N NaOH solution (80 mL), and ethyl acetate (80 mL) was shaken, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (80 mL x 2). The combined organic layers were dried over

anhydrous sodium sulfate, filtered, and evaporated to give free (*R*)-3-amino-1-(4-chlorobenzyl)pyrrolidine (3.35 g, 99%).

A solution of (*R*)-3-amino-1-(4-chlorobenzyl)pyrrolidine (3.35 g, 16 mmol) in $CH_2Cl_2$ (80 mL) was treated with $Et_3N$ (2.5 mL, 17.6 mmol), *N-tert*-butoxycarbonylglycine (2.79 g, 16.0 mmol), EDCI (3.07 g, 16.0 mmol) and HOBt (2.16 g, 16 mmol). After the reaction mixture was stirred at 25 °C for 16 h, 2 N NaOH solution (80 mL) was added. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (100 mL x 3). The combined organic layer was washed with water (100 mL x 2) and brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography ($SiO_2$, ethyl acetate) afforded the desired (*R*)-3-{*N*-(*tert*-butoxycarbonyl)glycyl}amino-1-(4-chlorobenzyl)pyrrolidine (5.40 g, 92%): $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.59 (s, 9 H), 1.53-1.65 (m, 1 H), 2.20-2.32 (m, 2 H), 2.55 (d, J = 5.1 Hz, 2 H)), 2.80-2.87 (m, 1 H), 3.56 (s, 2 H), 3.73 (d, J = 5.6 Hz, 2 H), 4.44 (br, 1 H), 5.23 (br, 1 H), 6.49 (br, 1 H), 7.23 (d, J = 8.3 Hz, 4 H), 7.28 (d, J = 8.3 Hz, 2 H).

**Reference Example 3: Preparation of (*R*)-1-(4-Chlorobenzyl)-3-(glycylamino)pyrrolidine.**

To a solution of (*R*)-3-{*N*-(*tert*-butoxycarbonyl)glycyl}amino-1-(4-chlorobenzyl)pyrrolidine (5.39 g, 14.7 mmol) in methanol (60 mL) was added 4 N HCl in dioxane (38 mL). The solution was stirred at room temperature for 2 h. The reaction mixture was concentrated and 2 N NaOH solution (80 mL) was added. The mixture was extracted with dichloromethane (80 mL x 3), and the combined extracts were dried over sodium sulfate and concentrated. Column chromatography ($SiO_2$, AcOEt/EtOH/$Et_3N$ = 90/5/5) gave (*R*)-3-(glycyl)amino-1-(4-chlorobenzyl)pyrrolidine (3.37 g, 86%): $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 1.77 (dd, J = 1.3 and 6.9 Hz, 1 H), 2.20-3.39 (m, 2 H), 2.53 (dd, J = 3.3 and 9.6 Hz, 1 H), 2.62 (dd, J = 6.6 and 9.6 Hz, 1 H), 2.78-2.87 (m, 1 H), 3.31 (s, 2 H), 3.57 (s, 2 H), 4.38-4.53 (br, 1 H), 7.18-7.32 (m, 4 H), 7.39 (br. s, 1 H).

Other 3-acylamino-1-(4-chlorobenzyl)pyrrolidines were also synthesized pursuant to methods of Reference Example 2 and 3 using the corresponding reactants respectively.

(*S*)-1-(4-Chlorobenzyl)-3-(glycylamino)pyrrolidine: 3.45 g, 79% (2 steps).

(*R*)-3-{(*S*)-Alanylamino}-1-(4-chlorobenzyl)pyrrolidine: 368 mg, 65% (2 steps).

(*R*)-3-{(*R*)-Alanylamino}-1-(4-chlorobenzyl)pyrrolidine: 425 mg, 75% (2 steps).

(*R*)-3-{(2*S*)-2-Amino-3-thienylpropanoyl}amino-1-(4-chlorobenzyl)pyrrolidine: 566 mg, 78% (2 steps).

(*R*)-3-{(2*R*)-2-Amino-3-thienylpropanoyl}amino-1-(4-chlorobenzyl)pyrrolidine: 585 mg, 81% (2 steps).

(*R*)-3-(2-Amino-2-methylpropanoyl)amino-1-(4-chlorobenzyl)pyrrolidine: 404 mg, 66% (2 steps).

(*R*)-3-{(2*S*)-2-Amino-4-(methylsulfonyl)butanoyl}amino-1-(4-chlorobenzyl)pyrrolidine: 535 mg, 72% (2 steps).

**Reference Example 4: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chlorobenzyl)pyrrolidine.**

A solution of (*R*)-1-(4-chlorobenzyl)-3-(glycylamino)pyrrolidine (7.36 g, 27.5 mmol) in $CH_2Cl_2$ (150 mL) was treated with $Et_3N$ (4.2 mL), 2-amino-5-(trifluoromethyl)benzoic acid (6.21 g, 30.3 mmol), EDCI (5.80 g, 30.3 mmol) and HOBt (4.09 g, 30.3 mmol). The reaction mixture was stirred at room temperature overnight. To the solution was added 2 N aqueous NaOH solution (2 mL x 2) and the mixture was extracted with $CH_2Cl_2$. The extract was washed with brine, dried over $Na_2SO_4$, and concentrated. Column chromatography ($SiO_2$, ethyl acetate to ethyl acetate/methanol = 9 : 1) afforded (*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-Chlorobenzyl)pyrrolidine (11.1 g, 89%): $^1H$ NMR (400 MHz, $CD_3OD$) δ 1.64-1.72 (m, 1 H), 2.20-2.30 (m, 1 H), 2.41-2.51 (m, 2 H), 2.71-2.78 (m, 2 H), 3.59 (dd, J = 15.4, 12.9 Hz, 2 H), 3.94 (s, 2 H), 4.35-4.41 (m, 1 H), 6.82 (d, J = 8.6 Hz, 1 H), 7.29 (s, 4 H), 7.40 (dd, J = 8.6, 1.7 Hz, 1 H), 7.85 (d, J = 0.96 Hz, 1 H); ESI/MS m/e 455.0 ($M^+$+H, $C_{21}H_{22}ClF_3N_4O_2$).

**Reference Example 5: Preparation of (*R*)-3-[{*N*-(2-(*tert*-Butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chlorobenzyl)pyrrolidine.**

A solution of (*R*)-1-(4-chlorobenzyl)-3-(glycylamino)pyrrolidine (5.0 g, 18.7 mmol) in dichloromethane (100 mL) was treated with $Et_3N$ (2.9 mL, 20.5 mmol), 2-(*tert*-butoxycarbonylamino)-5-(trifluoromethyl)benzoic acid (6.27 g, 20.5 mmol), EDCI (3.9 g, 20.5 mmol) and HOBt (2.8 g, 20.5 mmol). The reaction mixture was stirred at room temperature overnight. To the reaction mixture was added 2 N aqueous NaOH solution (80 mL) and the mixture was extracted with dichloromethane. The extract was dried over anhydrous $Na_2SO_4$, filtered, and evaporated. Column chromatography ($SiO_2$, hexane/ethyl acetate = 1/1-1/4)

afforded (*R*)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chlorobenzyl)pyrrolidine (9.41 g, 91%) as a white amorphous solid: ESI/MS m/e 555.2 ($M^+$+H, $C_{26}H_{30}ClF_3N_4O_4$).

**Reference Example 6: Preparation of (*R*)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine.**

A mixture of (*R*)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chlorobenzyl)pyrrolidine (6.3 g, 11.4 mmol), $Pd(OH)_2$ (1.68 g), $HCO_2H$ (3.7 mL), and methanol (80 mL) was stirred at 50 °C overnight. After the mixture was cooled to room temperature, the Pd catalyst was filtered off through Celite and the filtrate was concentrated. Column chromatography ($SiO_2$, AcOEt, AcOEt/MeOH = 5/1-4/1) gave (*R*)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (4.42 g, 90%) as a white solid: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.48 (s, 9 H), 2.0-2.4 (m, 2 H), 3.42-3.71 (m, 5 H), 4.00-4.22 (m, 2 H), 4.56 (br, 1 H), 7.48 (d, J = 9.0 Hz, 1 H), 7.93 (s, 1 H), 8.17 (br, 1 H), 8.33 (d, J = 9.0 Hz, 1 H), 8.45 (br, 1 H).

**Reference Example 7: Preparation of (*R*)-3-[{*N*-(2-*tert*-Butoxycarbonylamino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(3,4-methylenedioxybenzyl)pyrrolidine.**

To a mixture of (*R*)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (38.8 g), 3,4-methylenedioxybenzaldehyde (40.6 g),and 2.5% acetic acid in methanol (500 mL), was added $NaBH_3CN$ (22.7 g). The reaction mixture was stirred at 50 °C overnight. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure and water was added. The aqueous layer was adjusted to pH 10 with a 5 N agueous NaOH solution and the mixture was extractes with ethyl acetate (2 times). The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. Column chromatography ($SiO_2$, AcOEt/hexane = 3:1 to AcOEt/$CH_3OH$ = 9:1) gave (*R*)-3-[{*N*-(2-*tert*-butoxycarbonylamino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(3,4-methylenedioxybenzyl)pyrrolidine (30.2 g, 59%) as a white solid: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.50 (s, 9 H), 1.60-1.73 (m, 1 H), 2.25-2.45 (m, 2 H), 2.60-2.75 (m, 2 H), 2.87-3.00 (m, 1 H), 3.59 (s, 2 H), 4.05 (d, J = 4.7 Hz, 2 H), 4.48 (br, 1 H), 5.89 (s, 2 H), 6.64 (br, 1 H), 6.72 (s, 2 H), 6.80 (s, 1 H), 7.60 (d, J = 8.5 Hz, 1 H), 7.75 (br, 1 H), 7.81 (s, 1 H), 8.45 (d, J = 8.5 Hz, 1 H), 10.30 (s, 1 H).

**Reference Example 8: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(3,4-methylenedioxybenzyl)pyrrolidine.**

(*R*)-3-[{*N*-(2-*tert*-butoxycarbonylamino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(3,4-methylenedioxybenzyl)pyrrolidine (19 g) in dioxane (100 mL) was treated with 6 N HCl (100 mL). The mixture was stirred at room temperature overnight, adjusted to pH 10 with a 5 N aqueous NaOH solution, and extractes with ethyl acetate (3 times). The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated to give (*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(3,4-methylenedioxybenzyl)pyrrolidine (10.8 g, 69%): $^1$H NMR (400 MHz, $CDCl_3$) δ 1.56-1.66 (m, 1 H), 2.20-2.35 (m, 2 H), 2.48-2.54 (m, 1 H), 2.57-2.62 (m, 1 H), 2.81-2.89 (m, 1 H), 3.50 (s, 2 H), 4.01 (d, J = 5.1 Hz, 2 H), 4.40-4.50 (m, 1 H), 5.93 (s, 2 H), 6.56 (br.d, J = 8.0 Hz, 1 H), 6.68 (d, J = 8.8 Hz, 1 H), 6.72 (s, 2 H), 7.22 (br.t, J = 5.1 Hz, 1 H), 7.40 (d, J = 8.8 Hz, 1 H), 7.67 (s, 1 H).

**Reference Example 9: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-ethylbenzyl)pyrrolidine.**

(*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-ethylbenzyl)pyrrolidine was synthesized pursuant to methods of Reference Examples 7 and 8 using the corresponding reactant: 4.0 g, 34% (2 steps); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, J = 7.8 Hz, 3 H), 1.56-1.66 (m, 1 H), 2.22-2.32 (m, 2 H), 2.50-2.55 (m, 1 H), 2.59-2.66 (m, 3 H), 2.83-2.90 (m, 1 H), 3.56 (s, 2 H), 4.00 (d, J = 5.1 Hz, 2 H), 4.40-4.49 (m, 1 H), 6.55 (br.d, J = 8.0 Hz, 1 H), 6.66 (d, J = 8.6 Hz, 1 H), 7.12 (d, J = 8.3 Hz, 2 H), 7.19 (d, J = 8.3 Hz, 2 H), 7.40 (dd, J = 8.6 and 1.5 Hz, 1 H), 7.67 (d, J = 1.5 Hz, 1 H); The purity was determined by RPLC/MS (>99%).

**Reference Example 10: Preparation of (*R*)-3-[{*N*-(2-(*tert*-Butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-hydroxy-3-nitrobenzyl)pyrrolidine.**

To a mixture of (*R*)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (43.0 mg, 0.10 mmol), 4-hydroxy-3-nitrobenzaldehyde (33.4 mg, 0.20 mmol), and 2.5% acetic acid in methanol (2 mL) was added $NaBH_3CN$ (19 mg, 0.30 mmol). The reaction mixture was

stirred at 50 °C for 5 h. The mixture was cooled to room temperature, loaded onto Varian™ SCX column, and washed with $CH_3OH$. Product was eluted off using 2 N $NH_3$ in $CH_3OH$ and concentrated to afford (*R*)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-hydroxy-3-nitrobenzyl)pyrrolidine (56.5 mg, 97%): The purity was determined by RPLC/MS (98%); ESI/MS m/e 582.3 ($M^+$+H, $C_{26}H_{30}F_3N_5O_7$).

**Reference Example 11: Preparation of (*R*)-3-[{*N*-(2-(*tert*-Butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-methoxy-3-nitrobenzyl)pyrrolidine.**

(*R*)-3-[{*N*-(2-(*tert*-Butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-methoxy-3-nitrobenzyl)pyrrolidine was synthesized pursuant to methods of Reference Example 10 using the corresponding reactant: 52.5 mg, 88%; The purity was determined by RPLC/MS (83%); ESI/MS m/e 596.4 ($M^+$+H, $C_{27}H_{32}F_3N_5O_7$).

**Reference Example 12: Preparation of (*R*)-3-[{*N*-(2-(*tert*-Butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chloro-3-nitrobenzyl)pyrrolidine.**

(*R*)-3-[{*N*-(2-(*tert*-Butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chloro-3-nitrobenzyl)pyrrolidine was synthesized pursuant to methods of Reference Example 10 using the corresponding reactant: 41.2 mg, 69%; The purity was determined by RPLC/MS (79%); ESI/MS m/e 600.3 ($M^+$+H, $C_{26}H_{29}ClF_3N_5O_6$).

**Reference Example 13: Preparation of (*R*)-3-[{*N*-(2-(*tert*-Butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-methyl-3-nitrobenzyl)pyrrolidine.**

A solution of (*R*)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (43.0 mg, 0.10 mmol), 4-methyl-3-nitrobenzyl chloride (22.3 mg, 0.12 mmol), and triethylamine (0.042 mL) in DMF (2 mL) was stirred at room temperature overnight. The solvent was removed under reduced pressure. The residue was dissolved in methanol, loaded onto Varian™ SCX column, and washed with $CH_3OH$. Product was eluted off using 2 N $NH_3$ in $CH_3OH$ and concentrated to afford (*R*)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-methyl-3-nitrobenzyl)pyrrolidine (54.6 mg, 94%): The purity was determined by RPLC/MS (96%); ESI/MS m/e 580.3 ($M^+$+H, $C_{27}H_{32}F_3N_5O_6$).

**Reference Example 14: Preparation of (*R*)-3-[{*N*-(2-(*tert*-Butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chloro-2-nitrobenzyl)pyrrolidine.**

(*R*)-3-[{*N*-(2-(*tert*-Butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chloro-2-nitrobenzyl)pyrrolidine was synthesized pursuant to methods of Reference Example 13 using the corresponding reactant: 58.2 mg, 97%; The purity was determined by RPLC/MS (>99%); ESI/MS m/e 600.3 ($M^+$+H, $C_{26}H_{29}ClF_3N_5O_6$).

**Reference Example 15: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-methyl-3-nitrobenzyl)pyrrolidine.**

To a solution of (*R*)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-methyl-3-nitrobenzyl)pyrrolidine (52.3 mg) in methanol (1.5 mL) was added 4 M HCl in dioxane (1.5 mL). The solution was stirred at room temperature overnight. The solvent was removed under reduced pressure. The residue was dissolved in methanol, loaded onto Varian™ SCX column, and washed with $CH_3OH$. Product was eluted off using 2 N $NH_3$ in $CH_3OH$ and concentrated to afford (*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-methyl-3-nitrobenzyl)pyrrolidine (39.1 mg, 91%): The purity was determined by RPLC/MS (92%); ESI/MS m/e 480.4 ($M^+$+H, $C_{22}H_{24}F_3N_5O_4$).

**Reference Example 16: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-hydroxy-3-nitrobenzyl)pyrrolidine.**

(*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-hydroxy-3-nitrobenzyl)pyrrolidine was synthesized pursuant to methods of Reference Example 15 using the corresponding starting material: 32.4 mg, 69%; The purity was determined by RPLC/MS (97%); ESI/MS m/e 482.3 ($M^+$+H, $C_{21}H_{22}F_3N_5O_5$).

**Reference Example 17: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-methoxy-3-nitrobenzyl)pyrrolidine.**

(*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-methoxy-3-nitrobenzyl)pyrrolidine was synthesized pursuant to methods of Reference Example 15 using the corresponding starting material: 32.6 mg, 65%; The purity was determined by RPLC/MS (98%); ESI/MS m/e 496.3 ($M^+$+H, $C_{22}H_{24}F_3N_5O_5$).

**Reference Example 18: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chloro-3-nitrobenzyl)pyrrolidine.**

(*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chloro-3-nitrobenzyl)pyrrolidine was synthesized pursuant to methods of Reference Example 15 using the corresponding starting material: 28.8 mg, 84%; The purity was determined by RPLC/MS (89%); ESI/MS m/e 500.2 ($M^+$+H, $C_{21}H_{21}ClF_3N_5O_4$).

**Reference Example 18: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chloro-2-nitrobenzyl)pyrrolidine.**

(*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chloro-2-nitrobenzyl)pyrrolidine was synthesized pursuant to methods of Reference Example 15 using the corresponding starting material: 44.5 mg, 92%; The purity was determined by RPLC/MS (99%); ESI/MS m/e 500.2 ($M^+$+H, $C_{21}H_{21}ClF_3N_5O_4$).

**Reference Example 19: Preparation of (*R*)-1-(3-Amino-4-methylbenzyl)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine.**

A mixture of (*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-methyl-3-nitrobenzyl)pyrrolidine (39.1 mg), 10% Pd-activated carbon (8.6 mg), ammonium formate (103 mg) and isopropyl alcohol (2.0 mL) was stirred at room temperature overnight. The Pd catalyst was filtered off, and the filtrate was concentrated. The residue was dissolved in methanol, loaded onto Varian™ SCX column, and washed with $CH_3OH$. Product was eluted off using 2 N $NH_3$ in $CH_3OH$ and concentrated to afford (*R*)-1-(3-amino-4-methylbenzyl)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine: The purity was determined by RPLC/MS (>99%); ESI/MS m/e 450.4 ($M^+$+H, $C_{22}H_{26}F_3N_5O_2$).

**Reference Example 20: Preparation of (*R*)-1-(3-Amino-4-hydroxybenzyl)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine.**

(*R*)-1-(3-Amino-4-hydroxybenzyl)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine was synthesized pursuant to methods of Reference Example 19 using the corresponding starting material: The purity was determined by RPLC/MS (90%); ESI/MS m/e 452.3 ($M^+$+H, $C_{21}H_{24}F_3N_5O_3$).

**Reference Example 21: Preparation of (*R*)-1-(3-Amino-4-methoxybenzyl)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]pyr-**

trifluoromethylbenzoyl)glycyl}amino]pyrrolidine.

(*R*)-1-(3-Amino-4-methoxybenzyl)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine was synthesized pursuant to methods of Reference Example 19 using the corresponding starting material: The purity was determined by RPLC/MS (91%); ESI/MS m/e 466.3 ($M^+$+H, $C_{22}H_{26}F_3N_5O_3$).

**Reference Example 22: Preparation of (*R*)-1-(2-Amino-4-chlorobenzyl)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine.**

(*R*)-1-(2-Amino-4-chlorobenzyl)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine was synthesized pursuant to methods of Reference Example 19 using the corresponding starting material: The purity was determined by RPLC/MS (78%); ESI/MS m/e 470.2 ($M^+$+H, $C_{21}H_{23}ClF_3N_5O_2$).

**Reference Example 23: Preparation of (*R*)-1-(3-Amino-4-chlorobenzyl)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine.**

A mixture of (*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chloro-3-nitrobenzyl)pyrrolidine (28.8 mg), 10% Pd-activated carbon (6 mg), ammonium formate (73 mg), ethyl acetate (1.0 mL), and isopropyl alcohol (1.0 mL) was stirred at room temperature overnight. The Pd catalyst was filtered off, and the filtrate was concentrated. The residue was dissolved in methanol, loaded onto Varian™ SCX column, and washed with $CH_3OH$. Product was eluted off using 2 N $NH_3$ in $CH_3OH$ and concentrated to afford (*R*)-1-(3-amino-4-chlorobenzyl)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine: The purity was determined by RPLC/MS (69%); ESI/MS m/e 470.2 ($M^+$+H, $C_{21}H_{23}ClF_3N_5O_2$).

**Example 1: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-methyl-3-ureidobenzyl)pyrrolidine.**

A mixture of (*R*)-1-(3-amino-4-methylbenzyl)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (20 mg), potassium cyanate (10.8 mg), water (0.5 mL), dioxane (0.5 mL), and acetic acid (0.5 mL) was stirred at 55 °C for 1 h. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure. The residue was dissolved in methanol, loaded onto Varian™ SCX column, and washed with $CH_3OH$. Product was eluted off using 2 N $NH_3$ in $CH_3OH$ and concentrated to afford (*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-methyl-3-ureidobenzyl)pyrrolidine (20.5 mg. 94%): : The purity was determined by RPLC/MS (87%); ESI/MS m/e 493.1

($M^+$+H, $C_{23}H_{27}F_3N_6O_3$).

**Example 2: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-hydroxy-3-ureidobenzyl)pyrrolidine.**

(*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-hydroxy-3-ureidobenzyl)pyrrolidine was synthesized pursuant to methods of Example 1 using the corresponding starting material (23.1 mg, 83%): The purity was determined by RPLC/MS (78%); ESI/MS m/e 495.3 ($M^+$+H, $C_{22}H_{25}F_3N_6O_4$).

**Example 3: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-methoxy-3-ureidobenzyl)pyrrolidine.**

(*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-methoxy-3-ureidobenzyl)pyrrolidine was synthesized pursuant to methods of Example 1 using the corresponding starting material (15.0 mg, 45%): The purity was determined by RPLC/MS (85%); ESI/MS m/e 509.4 ($M^+$+H, $C_{23}H_{27}F_3N_6O_4$).

**Example 4: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chloro-3-ureidobenzyl)pyrrolidine.**

(*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chloro-3-ureidobenzyl)pyrrolidine was synthesized pursuant to methods of Example 1 using the corresponding starting material and purified by thin-layer chromatography: The purity was determined by RPLC/MS (93%); ESI/MS m/e 513.3 ($M^+$+H, $C_{22}H_{24}ClF_3N_6O_3$).

**Example 5: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(3-ethylureido)benzyl}pyrrolidine.**

A solution of (*R*)-1-(3-amino-4-methylbenzyl)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (20 mg) and ethyl isocyanate (0.0042 mL) in THF (1.5 mL) was stirred at 55 °C overnight. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure. The residue was dissolved in methanol, loaded onto Varian™ SCX column, and washed with $CH_3OH$. Product was eluted off using 2 N $NH_3$ in $CH_3OH$, concentrated, and purified by thin-layer chromatography to afford (*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(3-

ethylureido)benzyl}pyrrolidine: The purity was determined by RPLC/MS (94%); ESI/MS m/e 521.4 ($M^+$+H, $C_{25}H_{31}F_3N_6O_3$).

**Example 6: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(3-isopropylureido)benzyl}pyrrolidine.**

(*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(3-isopropylureido)benzyl}pyrrolidine was synthesized pursuant to methods of Example 5 using isopropyl isocyanate (0.0052 mL) as a reactant: The purity was determined by RPLC/MS (>99%); ESI/MS m/e 493.1 ($M^+$+H, $C_{26}H_{33}F_3N_6O_3$).

**Example 7: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-hydroxy-3-(3-isopropylureido)benzyl}pyrrolidine.**

(*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-hydroxy-3-(3-isopropylureido)benzyl}pyrrolidine was synthesized pursuant to methods of Example 5 using isopropyl isocyanate (0.0178 mL) as a reactant: The purity was determined by RPLC/MS (84%); ESI/MS m/e 537.5 ($M^+$+H, $C_{25}H_{31}F_3N_6O_4$).

**Example 8: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-ethylureido)-4-hydroxybenzyl}pyrrolidine.**

(*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-ethylureido)-4-hydroxybenzyl}pyrrolidine was synthesized pursuant to methods of Example 5 using ethyl isocyanate (0.0144 mL) as a reactant and purification was achieved with HPLC to give the desired compound as a TFA salt: The purity was determined by RPLC/MS (>99%); ESI/MS m/e 523.3 ($M^+$+H, $C_{24}H_{29}F_3N_6O_2$).

**Example 9: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(3-methyl-thioureido)benzyl}pyrrolidine.**

(*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(3-methyl-thioureido)benzyl}pyrrolidine was synthesized pursuant to methods of Example 5 using methyl isothiocyanate (19 mg) as a reactant and purification was achieved with HPLC to give the desired compound as a TFA salt: The purity was determined by RPLC/MS (77%); ESI/MS m/e 523.3 ($M^+$+H, $C_{24}H_{29}F_3N_6O_2S$).

**Example 10: Preparation of (*R*)-3-[{*N*-(2-Amino-5-**

trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-ethyl-thioureido)-4-methylbenzyl}pyrrolidine.

(*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-ethyl-thioureido)-4-methylbenzyl}pyrrolidine was synthesized pursuant to methods of Example 5 using ethyl isothiocyanate (0.0175 mL) as a reactant and purification was achieved with HPLC to give the desired compound as a TFA salt: The purity was determined by RPLC/MS (97%); ESI/MS m/e 537.4 ($M^+$+H, $C_{25}H_{31}F_3N_6O_2S$).

**Example 11: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-isopropyl-thioureido)-4-methylbenzyl}pyrrolidine.**

(*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-isopropyl-thioureido)-4-methylbenzyl}pyrrolidine was synthesized pursuant to methods of Example 5 using isopropyl isothiocyanate (0.030 mL) as a reactant and purification was achieved with HPLC to give the desired compound as a TFA salt: The purity was determined by RPLC/MS (73%); ESI/MS m/e 551.3 ($M^+$+H, $C_{26}H_{33}F_3N_6O_2S$).

**Example 12: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-chloro-3-(3-phenyl-thioureido)benzyl}pyrrolidine.**

(*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-chloro-3-(3-phenyl-thioureido)benzyl}pyrrolidine was synthesized pursuant to methods of Example 5 using phenyl isothiocyanate (0.050 mL) as a reactant and purification was achieved with HPLC to give the desired compound as a TFA salt: The purity was determined by RPLC/MS (96%); ESI/MS m/e 605.2 ($M^+$+H, $C_{28}H_{28}ClF_3N_6O_2S$).

**Example 13: Preparation of (*R*)-3-[{N-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(3-phenyl-thioureido)benzyl}pyrrolidine.**

(*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(3-phenyl-thioureido)benzyl}pyrrolidine was synthesized pursuant to methods of Example 5 using phenyl isothiocyanate (11.4 mg) as a reactant and purification was achieved with HPLC to give the desired compound as a TFA salt: The purity was determined by RPLC/MS (95%); ESI/MS m/e 585.3 ($M^+$+H, $C_{29}H_{31}F_3N_6O_2S$).

**Example 14: Preparation of (*R*)-3-[{*N*-(2-Amino-5-**

**trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1,1-dimethylureido)-4-hydroxylbenzyl}pyrrolidine.**

To a solution of (*R*)-1-(3-amino-4-hydroxy)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (30 mg) in THF (1.0 mL) was added *N,N*-dimethylcarbamoyl chrolide (0.0158 mL) and pyridine (1.0 mL). The mixture was stirred at 50 °C overnight. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure. The residue was dissolved in methanol, loaded onto Varian™ SCX column, and washed with $CH_3OH$. Product was eluted off using 2 N $NH_3$ in $CH_3OH$, concentrated, and purified by HPLC to afford (*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1,1-dimethylureido)-4-hydroxylbenzyl}pyrrolidine as a TFA salt: The purity was determined by RPLC/MS (>99%); ESI/MS m/e 523.3 ($M^+$+H, $C_{24}H_{29}F_3N_6O_4$).

**Example 15: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1,1-diethylureido)-4-methylbenzyl}pyrrolidine.**

(*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1,1-diethylureido)-4-methylbenzyl}pyrrolidine was synthesized pursuant to methods of Example 14 using N,N-diethylcarbamoyl chloride (0.0254 mL) as a reactant: The purity was determined by RPLC/MS (91%); ESI/MS m/e 549.3 ($M^+$+H, $C_{27}H_{35}F_3N_6O_3$).

**Example 16: Preparation of (*R*)-3-[{*N*-(2-Aamino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(1-pyrrolidinecarboxamido)benzyl}pyrrolidine.**

(*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(1-pyrrolidinecarboxamido)benzyl}pyrrolidine was synthesized pursuant to methods of Example 14 using 1-pyrrolidinecarbonyl chloride (0.0221 mL) as a reactant: The purity was determined by RPLC/MS (96%); ESI/MS m/e 547.3 ($M^+$+H, $C_{27}H_{33}F_3N_6O_3$).

**Example 17: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1,1-diethylureido)-4-hydroxybenzyl}pyrrolidine.**

(*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1,1-diethylureido)-4-hydroxybenzyl}pyrrolidine was synthesized pursuant to methods of Example 14 using *N,N*-diethylcarbamoyl chloride (0.0218 mL) as a reactant: The purity was determined by RPLC/MS (98%); ESI/MS m/e 551.4 ($M^+$+H, $C_{26}H_{33}F_3N_6O_4$).

**Example 18: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-hydroxy-3-(1-pyrrolidinecarboxamido)benzyl}pyrrolidine.**

(*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-hydroxy-3-(1-pyrrolidinecarboxamido)benzyl}pyrrolidine was synthesized pursuant to methods of Example 14 using 1-pyrrolidinecarbonyl chloride (0.0190 mL) as a reactant: The purity was determined by RPLC/MS (99%); ESI/MS m/e 549.4 ($M^+$+H, $C_{26}H_{31}F_3N_6O_4$).

**Example 19: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(4-morpholinecarboxamido)benzyl}pyrrolidine.**

(*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(4-morpholinecarboxamido)benzyl}pyrrolidine was synthesized pursuant to methods of Example 14 using 4-morpholinecarbonyl chloride (0.0156 mL) as a reactant: The purity was determined by RPLC/MS (99%); ESI/MS m/e 563.5 ($M^+$+H, $C_{27}H_{33}F_3N_6O_4$).

**Example 20: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1,1-dimethylureido)-4-methylbenzyl}pyrrolidine.**

(*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1,1-dimethylureido)-4-methylbenzyl}pyrrolidine was synthesized pursuant to methods of Example 14 using *N*,*N*-dimethylcarbamoyl chloride (0.0123 mL) as a reactant: The purity was determined by RPLC/MS (98%); ESI/MS m/e 521.3 ($M^+$+H, $C_{25}H_{31}F_3N_6O_3$).

**Example 21: Preparation of (*R*)-1-(4-Chlorobenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine.**

A suspension of (*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chlorobenzyl)pyrrolidine (22.7 mg, 0.05 mmol) and trimethylsilyl isocyanate (6.3 mg) in THF was stirred at 55 °C for 16 h. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure. The residue was dissolved in 5% trifluoroacetic acid in water (0.25 mL) for 5 min. Evaporation and purification with HPLC afforded (*R*)-1-(4-chlorobenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine: The purity was determined by RPLC/MS (95%); ESI/MS m/e 498.0 ($M^+$+H, $C_{22}H_{23}ClF_3N_5O_3$).

**Example 22: Preparation of (*R*)-1-(4-Chlorobenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine.**

A solution of (*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chlorobenzyl)pyrrolidine (30 mg, 0.066 mmol) and isopropyl isocyanate (28 mg, 0.33 mmol) in THF (0.5 mL) was stirred at 55 °C overnight. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure. The residue was dissolved in methanol, loaded onto Varian™ SCX column, and washed with $CH_3OH$. Product was eluted off using 2 N $NH_3$ in $CH_3OH$, concentrated, and purified by HPLC to afford (*R*)-1-(4-chlorobenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine: ESI/MS m/e 540.2 ($M^+$+H, $C_{25}H_{29}ClF_3N_5O_3$).

**Example 23: Preparation of (*R*)-3-[{*N*-(2-(3-Isopropylureido)-5-trifluoromethylbenzoyl)glycyl}amino]-1-(3,4-methylenedioxybenzyl)pyrrolidine.**

(*R*)-3-[{*N*-(2-(3-Isopropylureido)-5-trifluoromethylbenzoyl)glycyl}amino]-1-(3,4-methylenedioxybenzyl)pyrrolidine was synthesized pursuant to methods of Example 22 using the corresponding starting material: ESI/MS m/e 550.3 ($M^+$+H, $C_{26}H_{30}F_3N_5O_5$).

**Example 24: Preparation of (*R*)-1-(4-Ethylbenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine.**

(*R*)-1-(4-Ethylbenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine was synthesized pursuant to methods of Example 22 using the corresponding starting material: ESI/MS m/e 534.1 ($M^+$+H, $C_{27}H_{34}F_3N_5O_3$).

**Example 25: Preparation of (*R*)-1-(4-chlorobenzyl)-3-[{*N*-(2-(3-ethylureido)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine.**

(*R*)-1-(4-Ethylbenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine was synthesized pursuant to methods of Example 22 using ethyl isocyanate as a reactant: ESI/MS m/e 526.4 ($M^+$+H, $C_{24}H_{27}ClF_3N_5O_3$).

**Example 26: Preparation of (*R*)-3-[{*N*-(2-(3-Ethylureido)-5-trifluoromethylbenzoyl)glycyl}amino]-1-(3,4-**

methylenedioxybenzyl)pyrrolidine.

(*R*)-3-[{*N*-(2-(3-Ethylureido)-5-trifluoromethylbenzoyl)glycyl}amino]-1-(3,4-methylenedioxybenzyl)pyrrolidine was synthesized pursuant to methods of Example 22 using the corresponding starting material and ethyl isocyanate as a reactant: ESI/MS m/e 536.3 ($M^+$+H, $C_{25}H_{28}F_3N_5O_5$).

**Example 27: Preparation of (*R*)-1-(4-Ethylbenzyl)-3-[{*N*-(2-(3-ethylureido)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine.**

(*R*)-1-(4-Ethylbenzyl)-3-[{*N*-(2-(3-ethylureido)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine was synthesized pursuant to methods of Example 22 using the corresponding starting material and ethyl isocyanate as a reactant: ESI/MS m/e 520.3 ($M^+$+H, $C_{26}H_{32}F_3N_5O_3$).

**Example 28: Measurement of Inhibition of MIP-1α Binding to THP-1 Cells by Test Compounds.**

Human monocytic leukemia cell line THP-1 was suspended in assay buffer (RPMI-1640 (Gibco-BRL Co.) containing 0.1% BSA and 25 mM HEPES adjusted to pH 7.4) to give a cell suspension of a concentration of 1 x $10^7$ cells/mL. The test compound was diluted in the assay buffer and used as the test compound solution. Iodinated human MIP-1α (DuPont NEN Co.) was diluted in assay buffer to 250 nCi/mL and used as the labeled ligand solution. In a 96 well filter plate (Millipore Co.), 25 µL of test compound solution, 25 µL of labeled ligand solution and 50 µL of cell suspension were aliquoted into each well in this order, stirred (total reaction volume 100 µL), and incubated for one hour at 18 °C.

After the reaction, the reaction solution was filtered, and the filter was washed twice with 200 µL of cold PBS (200 µL of cold PBS was added and then filtered). The filter was air-dried and 25 µL of liquid scintillator was added into each well. The radioactivity retained by the cells on the filter were measured using TopCount (Packard Instrument Co.).

To calculate the ability of test compounds to inhibit binding of human MIP-1α to THP-1 cells, non-specific binding determined by adding 100 ng of unlabeled human MIP-1α (Peprotech Co.) in place of the test compound was subtracted, while the counts with no test compound added was taken as 100%.

Inhibition (%) = {1 - (A - B)/(C - B)} x 100

(A, counts with test compound added; B, counts with 100 ng of unlabeled human MIP-1α added; C, counts with [$^{125}$I]-labeled human MIP-1α added).

**Example 29: Measurement of Inhibition of MCP-1 Binding to THP-1 Cells.**

Human monocytic leukemia cell line THP-1 was suspended in assay buffer (50 mM HEPES, pH 7.4, 1.0 mM $CaCl_2$, 5.0 mM $MgCl_2$, 0.5% BSA) to give a cell suspension of a concentration of 1 x $10^7$ cells/mL. The test compound was diluted in the assay buffer and used as the test compound solution. [$^{125}$I]-labeled recombinant human MCP-1 (Amersham Pharmacia Biotech UK Ltd.) was diluted in assay buffer to 1 μCi/mL and used as the labeled ligand solution. In a 96 well filter plate (Millipore Co.), 25 μL of test compound solution, 25 μL of labeled ligand solution and 50 μL of cell suspension were aliquoted into each well in this order, stirred (total reaction volume 100 μL), and incubated for one hour at 18 °C.

After the reaction, the reaction solution was filtered, and the filter was washed twice with 150 μL of cold PBS (150 μL of cold PBS was added and then filtered). The filter was air-dried and 25 μL of liquid scintillator was added into each well. The radioactivity retained by the cells on the filter were measured using TopCount (Packard Instrument Co.).

To calculate the ability of test compound to inhibit binding of human MCP-1 to THP-1 cells, non-specific binding determined by adding 100 ng of unlabeled human MCP-1 in place of the test compound was subtracted, while the counts with no test compound added was taken as 100%.

Inhibition (%) = {1 - (A - B)/(C - B)} x 100

(A, counts with test compound added; B, counts with 100 ng of unlabeled human MCP-1 added; C, counts with [$^{125}$I]-labeled human MCP-1 added).

When inhibition by the ureido-substituted cyclic amine derivative of this invention was measured, for example, the following compounds demonstrated 40%-80% and >80% inhibitory activity at 1 μM, respectively. These compounds are

40%-80% inhibition at 1 μM:

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1-carbamoylureido)-4-hydroxybenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1-

carbamoylureido)-4-chlorobenzyl}pyrrolidine;
(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{2-(1-carbamoylureido)-4-chlorobenzyl}pyrrolidine;
(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1-carbamoylureido)-4-methylbenzyl}pyrrolidine;
(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-hydroxy-3-(3-isopropylureido)benzyl}pyrrolidine;
(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1,1-dimethylureido)-4-methylbenzyl}pyrrolidine;
(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1,1-dimethylureido)-4-hydroxylbenzyl}pyrrolidine;
(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1,1-diethylureido)-4-hydroxybenzyl}pyrrolidine; and
(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-hydroxy-3-(1-pyrrolidinecarboxamido)benzyl}pyrrolidine;

>80% inhibition at 1 μM:
(3*R*)-1-(4-chlorobenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;
(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1-carbamoylureido)-4-methoxybenzyl}pyrrolidine;
(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-hydroxy-3-ureidobenzyl)pyrrolidine;
(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-methoxy-3-ureidobenzyl)pyrrolidine;
(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-methyl-3-ureidobenzyl)pyrrolidine;
(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chloro-3-ureidobenzyl)pyrrolidine;
(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-ethylureido)-4-methylbenzyl}pyrrolidine;
(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-isopropylureido)-4-methylbenzyl}pyrrolidine;
(3*R*)-1-(4-chlorobenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;
(3*R*)-1-(4-chlorobenzyl)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;
(3*R*)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]-1-

(3,4-methylenedioxybenzyl)pyrrolidine;

(3*R*)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]-1-(3,4-methylenedioxybenzyl)pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(3-phenyl-thioureido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-ethylureido)-4-hydroxybenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(3-methyl-thioureido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(4-morpholinecarboxamido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-ethyl-thioureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1,1-diethylureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(1-pyrrolidinecarboxamido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-isopropyl-thioureido)-4-methylbenzyl}pyrrolidine; and

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-chloro-3-(3-phenyl-thioureido)benzyl}pyrrolidine.

**Example 30: Measurement of Inhibition of Binding of [$^{125}$I]-Labeled Human MCP-1 to Cells Expressing the MCP-1 Receptor.**

1. Derivation of cells expressing the MCP-1 receptor

cDNA fragment containing the MCP-1 receptor reported by S. Yamagami et al., Biochemical Biophysical Research Communications 1994, 202, 1156-1162) was cloned into the expression plasmid pCEP4 (Invitrogen Co.) at the NotI site, and the plasmid obtained was transfected into the human kidney epithelial cell line 293-EBNA using the Lipofectamine reagent (Gibco-BRL Co.). The cells were cultured in the presence of the selective agent (Hygromycin), and a stably expressing transfectant line was obtained. The expression of the receptor was confirmed by binding of [$^{125}$I]-labeled human MCP-1.

2. Measurement of inhibition of binding of [$^{125}$I]-labeled baculovirus expressed human MCP-1 to the MCP-1 receptor expressing cells

The MCP-1 receptor expressing cells on tissue culture dishes were scraped using a cell scraper and suspended in assay buffer (D-MEM(Gibco-BRL Co.)

containing 0.1% BSA and 25 mM HEPES adjusted to pH 7.4) to give a cell suspension of a concentration of 6 x $10^6$ cells/mL. The test compound was diluted in the assay buffer. The remainder of the procedure was as described in Example 29.

**Example 31: Measurement of Inhibition of Cell Chemotaxis.**

In order to determine the inhibition of cell chemotaxis by the compounds of this invention, we measured cell chemotaxis caused by monocyte chemotactic factor MCP-1 using the human monocytic leukemia cell line THP-1 as the chemotactic cell according to the method of Fall et al. (J. Immunol. Methods, 190, 33, 239-247). 2 x $10^6$ cells/mL of THP-1 cells (suspended in RPMI-1640 (Flow Laboratories Co.) + 10% FCS) was placed in the upper chamber (200 µL) of a 96 well micro-chemotaxis chamber (Neuroprobe, registered tradename), and human recombinant MCP-1 in a same solution (Peprotech Co.) at a final concentration of 20 ng/mL was placed in the lower chamber, with a polycarbonate filter (PVP-free, Neuroprobe; registered tradename) placed between the two chambers. These were incubated at 37 °C for 2 hr in 5% $CO_2$.

The filter was removed, and the cells which had migrated to the underside of the filter was fixed, stained using Diff Quick (Kokusai Shiyaku Co.) and then quantitated using a plate reader (Molecular Device Co.) at a wavelength of 550 nm to determine the index of cell migration as a mean of 3 wells. In addition, test compounds were placed in the upper and lower chambers along with THP-1 and MCP-1, respectively, and the inhibition of cell migration (inhibition $IC_{50}$ (µM)) was determined. Inhibition was defined as {(cells migration induced MCP-1 with no test compound in the upper and lower chambers) - (cells migration with no MCP-1 added in the lower chamber) = 100%}, and the concentration of the test compound which gave 50% inhibition was designated $IC_{50}$.

When inhibition by the cyclic amine derivative of this invention was measured, for example, the 50% inhibition concentration ($IC_{50}$) for the following compounds were $IC_{50}$ < 0.1 µM.

$IC_{50}$ < 0.1 µM:

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chloro-3-ureidobenzyl)pyrrolidine;

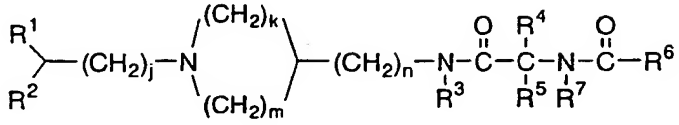
(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-isopropylureido)-4-methylbenzyl}pyrrolidine; and

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-ethyl-thioureido)-4-methylbenzyl}pyrrolidine.

## Claims

What is claimed is:

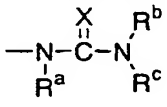
1. A compound of the formula (I) below:



(I)

, a pharmaceutically acceptable acid addition salt thereof or a pharmaceutically acceptable $C_1$-$C_6$ alkyl addition salt thereof,

wherein $R^1$ is a phenyl group or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, in which the phenyl or aromatic heterocyclic group may be condensed with a benzene ring or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, to form a condensed ring, and the phenyl group, aromatic heterocyclic group, or condensed ring may be substituted with one or more of a group represented by the formula:



a halogen atom, a hydroxy group, a cyano group, a nitro group, a carboxy group, a carbamoyl group, a $C_1$-$C_6$ alkyl group, a $C_3$-$C_8$ cycloalkyl group, a $C_2$-$C_6$ alkenyl group, a $C_1$-$C_6$ alkoxy group, a $C_1$-$C_6$ alkylthio group, a $C_2$-$C_4$ alkylenoxy group, a $C_1$-$C_3$ alkylenedioxy group, a phenyl group, a phenoxy group, a phenylthio group, a benzyl group, a benzyloxy group, a benzoylamino group, a 3-phenylureido group, a 3-phenyl-thioureido group, a $C_2$-$C_7$ alkanoyl group, a $C_2$-$C_7$ alkoxycarbonyl group, a $C_2$-$C_7$ alkanoyloxy group, a $C_2$-$C_7$ alkanoylamino group, a $C_1$-$C_6$ alkylsulfonyl group, a *N*-phenylcarbamoyl group, an amino group, a mono($C_1$-$C_6$ alkyl)amino group, or a di($C_1$-$C_6$ alkyl)amino group, wherein the substituent for the phenyl group, $C_3$-$C_8$ cycloalkyl group, aromatic heterocyclic group, or condensed ring is optionally substituted with one or more of a halogen atom, a hydroxy group, an amino group, a trifluoromethyl group, a $C_1$-$C_6$ alkyl group, or a $C_1$-$C_6$ alkoxy group;

$R^a$, $R^b$, and $R^c$ are the same or different from each other and are a hydrogen atom, a $C_1$-$C_6$ alkyl group, a carbamoyl group, or $R^b$ and $R^c$ taken together with the adjacent nitrogen atom form a pyrrolidine, a piperidine, a morpholine, a

thiomoropholine, or a hexamethyleneimine;

X is a oxygen atom or a sulfur atom;

$R^2$ is a hydrogen atom or a $C_1$-$C_6$ alkyl group;

j represents an integer of 0-2;

k represents an integer of 0-2;

m represents an integer of 2-4;

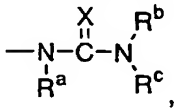
n represents 0 or 1;

$R^3$ is a hydrogen atom or a $C_1$-$C_6$ alkyl group;

$R^4$ and $R^5$ are the same or different from each other and are a hydrogen atom, a phenyl group, or a $C_1$-$C_6$ alkyl group, in which the $C_1$-$C_6$ alkyl group is optionally substituted with one or more of a halogen atom, a hydroxy group, a cyano group, a nitro group, a carboxy group, a carbamoyl group, a mercapto group, a guanidino group, a $C_3$-$C_8$ cycloalkyl group, a $C_1$-$C_6$ alkoxy group, a $C_1$-$C_6$ alkylthio group, a phenyl group optionally substituted with one or more of a halogen atom, a hydroxy group, a $C_1$-$C_6$ alkyl group, a $C_1$-$C_6$ alkoxy group, or a benzyloxy group, a phenoxy group, a benzyloxy group, a benzyloxycarbonyl group, a $C_2$-$C_7$ alkanoyl group, a $C_2$-$C_7$ alkoxycarbonyl group, a $C_2$-$C_7$ alkanoyloxy group, a $C_2$-$C_7$ alkanoylamino group, a $C_1$-$C_6$ alkylsulfonyl group, an amino group, a mono($C_1$-$C_6$ alkyl)amino group, a di($C_1$-$C_6$ alkyl)amino group, or an aromatic heterocyclic group having 1-3 of heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof and optionally condensed with benzene ring, or $R^4$ and $R^5$ taken together form a 3 to 6 membered cyclic hydrocarbon;

$R^7$ is a hydrogen atom or a $C_1$-$C_6$ alkyl group, or $R^7$ taken together with $R^5$ represents $C_2$-$C_5$ alkylene group;

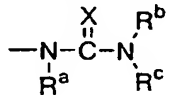
$R^6$ is a phenyl group or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, in which the phenyl or aromatic heterocyclic group may be condensed with a benzene ring or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, to form a condensed ring, and the phenyl group, aromatic heterocyclic group, or condensed ring may be substituted with one or more of a group represented by the formula:



a halogen atom, a hydroxy group, a mercapto group, a cyano group, a nitro group,

a thiocyanato group, a carboxy group, a carbamoyl group, a trifluoromethyl group, a $C_1$-$C_6$ alkyl group, a $C_3$-$C_6$ cycloalkyl group, a $C_2$-$C_6$ alkenyl group, a $C_1$-$C_6$ alkoxy group, a $C_3$-$C_8$ cycloalkyloxy group, a $C_1$-$C_6$ alkylthio group, a $C_1$-$C_3$ alkylenedioxy group, a phenyl group, a phenoxy group, a benzyl group, a benzoyl group, a phenylsulfinyl group, a phenylsulfonyl group, a 3-phenylureido group, a 3-phenyl-thioureido group, a $C_2$-$C_7$ alkanoyl group, a $C_2$-$C_7$ alkoxycarbonyl group, a $C_2$-$C_7$ alkanoyloxy group, a $C_2$-$C_7$ alkanoylamino group, a $C_1$-$C_6$ alkylsulfonyl group, an amino group, a mono($C_1$-$C_6$ alkyl)amino group, a di($C_1$-$C_6$ alkyl)amino group, a $C_2$-$C_7$ (alkoxycarbonyl)amino group, or a $C_1$-$C_6$ (alkylsulfonyl)amino group, wherein the substituent for the phenyl group, aromatic heterocyclic group, or condensed ring is optionally substituted with one or more of a halogen atom, a cyano group, a hydroxy group, an amino group, trifluoromethyl group, a $C_1$-$C_6$ alkyl group, a $C_1$-$C_6$ alkoxy group, a $C_1$-$C_6$ alkylthio group, a mono($C_1$-$C_6$ alkyl)amino group, or a di($C_1$-$C_6$ alkyl)amino group;

provided that the phenyl group, aromatic heterocyclic group, or condensed ring in at least one of $R^1$ and $R^6$ is substituted with a 3-phenyl-thioureido group or a group represented by the formula:



2. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable $C_1$-$C_6$ alkyl addition salt as set forth in claim 1, wherein k = 1 and m = 2 in the above formula (I).

3. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable $C_1$-$C_6$ alkyl addition salt as set forth in claim 2, wherein n = 0 in the above formula (I).

4. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable $C_1$-$C_6$ alkyl addition salt as set forth in claim 1, wherein k = 0, m = 3 and n = 1 in the above formula (I).

5. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable $C_1$-$C_6$ alkyl addition salt as set forth in claim 1, wherein k = 1 and m = 3 in the above formula (I).

6. A compound, its pharmaceutically acceptable acid addition salt or its

pharmaceutically acceptable $C_1$-$C_6$ alkyl addition salt as set forth in claim 1, wherein k = 2 and m = 2 in the above formula (I).

7. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable $C_1$-$C_6$ alkyl addition salt as set forth in claim 6, wherein n = 1 in the above formula (I).

8. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable $C_1$-$C_6$ alkyl addition salt as set forth in claim 1, wherein k = 1 and m = 4 in the above formula (I).

9. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable $C_1$-$C_6$ alkyl addition salt as set forth in claim 1, wherein j = 0 in the above formula(I).

10. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable $C_1$-$C_6$ alkyl addition salt as set forth in claim 1, wherein $R^2$ is a hydrogen atom, $R^3$ is a hydrogen atom and $R^7$ is a hydrogen atom in the above formula (I).

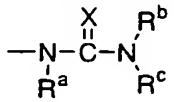
11. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable $C_1$-$C_6$ alkyl addition salt as set forth in claim 1, wherein $R^a$ is a hydrogen atom, $R^b$ is a hydrogen atom and $R^c$ is a hydrogen atom in the above formula (I).

12. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable $C_1$-$C_6$ alkyl addition salt as set forth in claim 1, wherein the substituent for the phenyl group, aromatic heterocyclic group, or condensed ring in $R^1$ is one or more of a halogen atom, a hydroxy group, a $C_1$-$C_6$ alkyl group, a $C_2$-$C_6$ alkenyl group, a $C_1$-$C_6$ alkoxy group, a $C_1$-$C_6$ alkylthio group, a $C_2$-$C_4$ alkylenoxy group, a methylenedioxy group, a *N*-phenylcarbamoyl group, an amino group, a mono($C_1$-$C_6$ alkyl)amino group, or a di($C_1$-$C_6$ alkyl)amino group in the above formula (I).

13. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable $C_1$-$C_6$ alkyl addition salt as set forth in claim 1, wherein the substituent for the phenyl group, aromatic heterocyclic group, or condensed ring in $R^6$ is one or more of a halogen atom, a nitro group, a

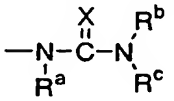
trifluoromethyl group, a $C_1$-$C_6$ alkyl group, a $C_1$-$C_6$ alkoxy group, a phenylsulfonyl group, a $C_2$-$C_7$ alkanoylamino group, an amino group or a trifluoromethoxy group in the above formula (I).

14. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable $C_1$-$C_6$ alkyl addition salt as set forth in claim 1, wherein $R^1$ is a phenyl group substituted with a group represented by the formula:



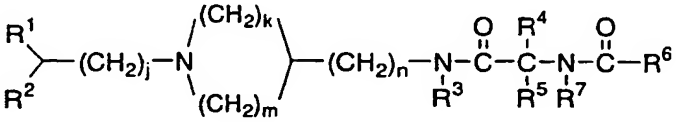
in the above formula (I).

15. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable $C_1$-$C_6$ alkyl addition salt as set forth in claim 1, wherein $R^6$ is a phenyl group substituted with a group represented by the formula:



in the above formula (I).

16. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell using a pharmaceutical preparation containing a therapeutically effective amount of a compound represented by the formula (I) below:

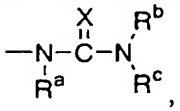


(I)

, a pharmaceutically acceptable acid addition salt thereof or a pharmaceutically acceptable $C_1$-$C_6$ alkyl addition salt thereof,

wherein $R^1$ is a phenyl group or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, in which the phenyl or aromatic heterocyclic group may be condensed with a benzene ring or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, to form a condensed ring, and the phenyl group, aromatic heterocyclic group, or condensed ring may be substituted with one or more of a group represented

by the formula:



a halogen atom, a hydroxy group, a cyano group, a nitro group, a carboxy group, a carbamoyl group, a $C_1$-$C_6$ alkyl group, a $C_3$-$C_8$ cycloalkyl group, a $C_2$-$C_6$ alkenyl group, a $C_1$-$C_6$ alkoxy group, a $C_1$-$C_6$ alkylthio group, a $C_2$-$C_4$ alkylenoxy group, a $C_1$-$C_3$ alkylenedioxy group, a phenyl group, a phenoxy group, a phenylthio group, a benzyl group, a benzyloxy group, a benzoylamino group, a $C_2$-$C_7$ alkanoyl group, a $C_2$-$C_7$ alkoxycarbonyl group, a $C_2$-$C_7$ alkanoyloxy group, a $C_2$-$C_7$ alkanoylamino group, a $C_1$-$C_6$ alkylsulfonyl group, a *N*-phenylcarbamoyl group, an amino group, a mono($C_1$-$C_6$ alkyl)amino group, or a di($C_1$-$C_6$ alkyl)amino group, wherein the substituent for the phenyl group, $C_3$-$C_8$ cycloalkyl group, aromatic heterocyclic group, or condensed ring is optionally substituted with one or more of a halogen atom, a hydroxy group, an amino group, a trifluoromethyl group, a $C_1$-$C_6$ alkyl group, or a $C_1$-$C_6$ alkoxy group;

$R^a$, $R^b$, and $R^c$ are the same or different from each other and are a hydrogen atom, a $C_1$-$C_6$ alkyl group, a carbamoyl group, or $R^b$ and $R^c$ taken together with the adjacent nitrogen atom form a pyrrolidine, a piperidine, a morpholine, a thiomoropholine, or a hexamethyleneimine;

X is a oxygen atom or a sulfur atom;

$R^2$ is a hydrogen atom or a $C_1$-$C_6$ alkyl group;

j represents an integer of 0-2;

k represents an integer of 0-2;

m represents an integer of 2-4;

n represents 0 or 1;

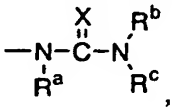
$R^3$ is a hydrogen atom or a $C_1$-$C_6$ alkyl group;

$R^4$ and $R^5$ are the same or different from each other and are a hydrogen atom, a phenyl group, or a $C_1$-$C_6$ alkyl group, in which the $C_1$-$C_6$ alkyl group is optionally substituted with one or more of a halogen atom, a hydroxy group, a cyano group, a nitro group, a carboxy group, a carbamoyl group, a mercapto group, a guanidino group, a $C_3$-$C_8$ cycloalkyl group, a $C_1$-$C_6$ alkoxy group, a $C_1$-$C_6$ alkylthio group, a phenyl group optionally substituted with one or more of a halogen atom, a hydroxy group, a $C_1$-$C_6$ alkyl group, a $C_1$-$C_6$ alkoxy group, or a benzyloxy group, a phenoxy group, a benzyloxy group, a benzyloxycarbonyl group, a $C_2$-$C_7$ alkanoyl group, a $C_2$-$C_7$ alkoxycarbonyl group, a $C_2$-$C_7$ alkanoyloxy group, a $C_2$-$C_7$ alkanoylamino group, a $C_1$-$C_6$ alkylsulfonyl group, an amino group, a mono($C_1$-$C_6$ alkyl)amino group, a di($C_1$-$C_6$ alkyl)amino group, or an aromatic heterocyclic

group having 1-3 of heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof and optionally condensed with benzene ring, or $R^4$ and $R^5$ taken together form a 3 to 6 membered cyclic hydrocarbon;

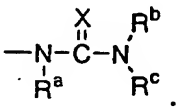
$R^7$ is a hydrogen atom or a $C_1$-$C_6$ alkyl group, or $R^7$ taken together with $R^5$ represents $C_2$-$C_5$ alkylene group;

$R^6$ is a phenyl group or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, in which the phenyl or aromatic heterocyclic group may be condensed with a benzene ring or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, to form a condensed ring, and the phenyl group, aromatic heterocyclic group, or condensed ring may be substituted with one or more of a group represented by the formula:



a halogen atom, a hydroxy group, a mercapto group, a cyano group, a nitro group, a thiocyanato group, a carboxy group, a carbamoyl group, a trifluoromethyl group, a $C_1$-$C_6$ alkyl group, a $C_3$-$C_6$ cycloalkyl group, a $C_2$-$C_6$ alkenyl group, a $C_1$-$C_6$ alkoxy group, a $C_3$-$C_8$ cycloalkyloxy group, a $C_1$-$C_6$ alkylthio group, a $C_1$-$C_3$ alkylenedioxy group, a phenyl group, a phenoxy group, a benzyl group, a benzoyl group, a phenylsulfinyl group, a phenylsulfonyl group, a 3-phenylureido group, a $C_2$-$C_7$ alkanoyl group, a $C_2$-$C_7$ alkoxycarbonyl group, a $C_2$-$C_7$ alkanoyloxy group, a $C_2$-$C_7$ alkanoylamino group, a $C_1$-$C_6$ alkylsulfonyl group, an amino group, a mono($C_1$-$C_6$ alkyl)amino group, a di($C_1$-$C_6$ alkyl)amino group, a $C_2$-$C_7$ (alkoxycarbonyl)amino group, or a $C_1$-$C_6$ (alkylsulfonyl)amino group, wherein the substituent for the phenyl group, aromatic heterocyclic group, or condensed ring is optionally substituted with one or more of a halogen atom, a cyano group, a hydroxy group, an amino group, trifluoromethyl group, a $C_1$-$C_6$ alkyl group, a $C_1$-$C_6$ alkoxy group, a $C_1$-$C_6$ alkylthio group, a mono($C_1$-$C_6$ alkyl)amino group, or a di($C_1$-$C_6$ alkyl)amino group;

provided that the phenyl group, aromatic heterocyclic group, or condensed ring in at least one of $R^1$ and $R^6$ is substituted with a group represented by the formula:



17. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein k = 1 and m = 2 in the above formula (I).

18. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 17, wherein n = 0 in the above formula (I).

19. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein k = 0, m = 3 and n = 1 in the above formula (I).

20. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein k =1 and m = 3 in the above formula (I).

21. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein k = 2 and m = 2 in the above formula (I).

22. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 21, wherein n = 1 in the above formula (I).

23. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein k = 1 and m = 4 in the above formula (I).

24. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein j = 0 in the above formula (I).

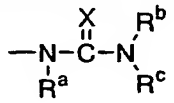
25. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein $R^2$ is a hydrogen atom, $R^3$ is a hydrogen atom and $R^7$ is a hydrogen atom in the above formula (I).

26. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein $R^a$ is a hydrogen atom, $R^b$ is a hydrogen atom and $R^c$ is a hydrogen atom in the above formula (I).

27. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in Claim 16, wherein the substituent for the phenyl group, aromatic heterocyclic group, or condensed ring in $R^1$ is one or more of a halogen atom, a hydroxy group, a $C_1$-$C_6$ alkyl group, a $C_2$-$C_6$ alkenyl group, a $C_1$-$C_6$ alkoxy group, a $C_1$-$C_6$ alkylthio group, a $C_2$-$C_4$ alkylenoxy group, a methylenedioxy group, a *N*-phenylcarbamoyl group, an amino group, a mono($C_1$-$C_6$ alkyl)amino group, or a di($C_1$-$C_6$ alkyl)amino group in the above formula (I).

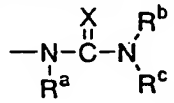
28. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein the substituent for the phenyl group, aromatic heterocyclic group, or condensed ring in $R^6$ is one or more of a halogen atom, a nitro group, a trifluoromethyl group, a $C_1$-$C_6$ alkyl group, a $C_1$-$C_6$ alkoxy group, a phenylsulfonyl group, a $C_2$-$C_7$ alkanoylamino group, an amino group or a trifluoromethoxy group in the above formula (I).

29. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein $R^1$ is a phenyl group substituted with a 3-phenyl-thioureido group or a group represented by the formula:



in the above formula (I).

30. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein $R^6$ is a phenyl group substituted with a 3-phenyl-thioureido group or a group represented by the formula:



in the above formula (I).

31. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein the chemokine is MCP-1.

32. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein the chemokine receptor is CCR2A or CCR2B.

33. A method of treating a disease, in which a chemokine is implicated, which comprises administering a pharmaceutical preparation containing a therapeutically effective amount of a compound represented by the formula (I) as defined in claim 1.

34. A method of treating a disease as set forth in claim 33, wherein the disease is rheumatoid arthritis.

35. A method of treating a disease as set forth in claim 33, wherein the disease is multiple sclerosis.

36. A method of treating a disease as set forth in claim 33, wherein the disease is nephritis or nephropathy.

37. A method of treating a disease as set forth in claim 33, wherein the disease is atherosclerosis.

38. A method of treating a disease as set forth in claim 33, wherein the chemokine is MCP-1.

39 A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable $C_1$-$C_6$ alkyl addition salt as set forth in claim 1, wherein the compound is:

(3*R*)-1-(4-chlorobenzyl)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-chlorobenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-ethylbenzyl)-3-[{*N*-(2-(3-ethylureido)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-1-(4-ethylbenzyl)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine;

(3*R*)-3-[{*N*-(2-(3-ethylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]-1-(3,4-methylenedioxybenzyl)pyrrolidine;

(3*R*)-3-[{*N*-(2-(3-isopropylureido)-5-(trifluoromethyl)benzoyl)glycyl}amino]-1-(3,4-methylenedioxybenzyl)pyrrolidine;

(3*R*)-1-(4-chlorobenzyl)-3-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}amino]pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{2-(1-carbamoylureido)-4-chlorobenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chloro-3-ureidobenzyl)pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1-carbamoylureido)-4-chlorobenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-chloro-3-(3-phenyl-thioureido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-methyl-3-ureidobenzyl)pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-ethylureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-isopropylureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1-carbamoylureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1,1-dimethylureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1,1-diethylureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(1-pyrrolidinecarboxamido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(4-morpholinecarboxamido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(3-methyl-thioureido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-ethyl-thioureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-isopropyl-thioureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-methyl-3-(3-phenyl-thioureido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{3-(3-ethylureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{3-(3-isopropylureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{3-(1-carbamoylureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{3-(1,1-dimethylureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{3-(1,1-diethylureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{4-methyl-3-(1-pyrrolidinecarboxamido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{4-methyl-3-(1-piperidinecarboxamido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{4-methyl-3-(4-morpholinecarboxamido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{4-methyl-3-(4-thiomorpholinecarboxamido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{4-methyl-3-(3-methyl-thioureido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{3-(3-ethyl-thioureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{3-(3-isopropyl-thioureido)-4-methylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-{4-methyl-3-(3-phenyl-thioureido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-methoxy-3-ureidobenzyl)pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1-carbamoylureido)-4-methoxybenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-hydroxy-3-ureidobenzyl)pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(3-ethylureido)-4-hydroxybenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-hydroxy-3-(3-isopropylureido)benzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1-carbamoylureido)-4-hydroxybenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1,1-dimethylureido)-4-hydroxylbenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{3-(1,1-diethylureido)-4-hydroxybenzyl}pyrrolidine;

(3*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-hydroxy-3-(1-pyrrolidinecarboxamido)benzyl}pyrrolidine;

1-(4-chlorobenzyl)-4-[{*N*-(5-trifluoromethyl-2-ureidobenzoyl)glycyl}aminomethyl]piperidine;

1-(4-chlorobenzyl)-4-[{*N*-(4,5-difluoro-2-ureidobenzoyl)glycyl}aminomethyl]piperidine;

4-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}aminomethyl]-1-(4-chloro-2-ureidobenzyl)piperidine;

4-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}aminomethyl]-1-(4-chloro-3-ureidobenzyl)piperidine;

4-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}aminomethyl]-1-(4-methyl-3-ureidobenzyl)piperidine;

4-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}aminomethyl]-1-(4-methoxy-3-ureidobenzyl)piperidine; or

4-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}aminomethyl]-1-(4-hydroxy-3-ureidobenzyl)piperidine.

# INTERNATIONAL SEARCH REPORT

Interr. ıal Application No
PCT/US 00/06714

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D207/09 C07D207/14 C07D211/34 C07D211/56 A61K31/40
A61K31/435 A61P29/00 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropnate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| P,A | WO 99 25686 A (TEIJIN LIMITED) 27 May 1999 (1999-05-27) claims 1-54 --- | 1-39 |
| A | WO 98 50534 A (SMITHKLINE BEECHAM CORPORATION) 12 November 1998 (1998-11-12) page 1 -page 13, line 8 --- | 1-39 |
| A | WO 98 31364 A (MERCK & CO., INC.) 23 July 1998 (1998-07-23) cited in the application the whole document --- | 1-39 |
| A | WO 98 25617 A (MERCK& CO., INC.) 18 June 1998 (1998-06-18) cited in the application claims 1-19 --- | 1-39 |

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 23 October 2000 | 30/10/2000 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Kyriakakou, G |

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Intern ial Application No
PCT/US 00/06714

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 97 44329 A (TEIJIN LIMITED)<br>27 November 1997 (1997-11-27)<br>cited in the application<br>the whole document | 1-39 |
| A | PATENT ABSTRACTS OF JAPAN<br>vol. 1995, no. 09,<br>31 October 1995 (1995-10-31)<br>& JP 07 145060 A (TEIJIN LTD),<br>6 June 1995 (1995-06-06)<br>abstract | 1-39 |

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

information on patent family members

Interr ıal Application No
PCT/US 00/06714

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9925686 A | 27-05-1999 | AU 1374199 A | 07-06-1999 |
| | | EP 1030840 A | 30-08-2000 |
| | | NO 20002486 A | 18-07-2000 |
| WO 9850534 A | 12-11-1998 | AU 7288598 A | 27-11-1998 |
| | | BR 9808502 A | 23-05-2000 |
| | | CN 1255162 T | 31-05-2000 |
| | | EP 0991753 A | 12-04-2000 |
| | | NO 995433 A | 05-11-1999 |
| | | ZA 9803843 A | 09-11-1998 |
| WO 9831364 A | 23-07-1998 | AU 6133098 A | 07-08-1998 |
| | | EP 1003743 A | 31-05-2000 |
| | | US 6124319 A | 26-09-2000 |
| WO 9825617 A | 18-06-1998 | AU 5522498 A | 03-07-1998 |
| WO 9744329 A | 27-11-1997 | JP 9309877 A | 02-12-1997 |
| | | AU 3135497 A | 09-12-1997 |
| | | EP 0914319 A | 12-05-1999 |
| JP 07145060 A | 06-06-1995 | NONE | |